IN THE MATTER OF THE UNITED STATES PATENT APPLICATION SERIAL NO. 10/020,882 IN FAVOUR OF SHELDON WILLIAM TOBE, APPLICANT AND THE INVENTOR OF THE SUBJECT MATTER THEREIN, FILED December 19, 2001.

DECLARATION

I, Sheldon William Tobe, M.D., Staff Nephrologist, Sunnybrook and Women's Health Sciences Centre and Associate Professor of Medicine, University of Toronto. DO SOLEMNLY DECLARE AND AFFIRM THE FOLLOWING:

1. I am currently a Staff Nephrologist, Sunnybrook and Women's Health Sciences Centre in Toronto, Ontario Canada. I am also an Associate Professor of Medicine at the University of Toronto. A copy of my curriculum vitae is attached as **Exhibit A** to this my Declaration. The focus of my professional activities is clearly set out in Exhibit A. I hold a MD from the University of Calgary, Alberta, Canada, as of June 5, 1985 and a B.Sc. (Honours Biochemistry), as of June 1982 from the University of Toronto, Ontario, Canada. As such I believe I am well qualified to comment and provide opinion in these matters.

2. The following paragraphs contain my comments and opinions concerning the United States Patent Office Examiner's Action dated August 11, 2005 (hereafter referred to as the Action) concerning U.S. Patent Application No. 10/020,882 entitled "STERILE LOW BICARBONATE DIALYSIS CONCENTRATE " (hereafter referred to as the '882 patent application).

3. I was asked by Neil H. Hughes, Patent Agent of the firm Ivor M. Hughes, Barristers and Solicitors, Patent and Trade Mark Agents to provide my opinion concerning the position taken by the United States Patent Office Examiner in the Action and his rejection of claims 1, 9-10, 14 and 17 of the '882 patent application. In particular, I was asked to provide my opinion with respect to the Examiner's allegation that pending claims 1, 9, 14 and 17 are allegedly anticipated by Purcell et al. (US 5,945,449), and that claim 17 is allegedly anticipated by Mahiout (US 6,492,336) and that Claim 14 is allegedly anticipated and Claims 1, 9-10, 14 and 17 are allegedly obvious in view of Koo et al. (previously cited as Chemical Abstracts 124:325351) and that Claims 1, 9-10, 14 and 17 are allegedly unpatentable over Martis et al. (WO 96/01118) in view of Purcell et al. I have met with our Agent and have instructed him as to what amendments would

be appropriate in view of the U.S. Examiner's allegations. The claims in the application have therefore been amended to identify over any of the references cited for the following reasons.

4. In my opinion, the inventions described in amended claims 1, 9, 14, 17, and 18-23 in the '882 patent application are not anticipated nor rendered obvious in light of the teachings and disclosures of the above-mentioned prior art. I thus disagree with the conclusions reached by the Examiner in the Action with respect to the '882 patent application. I describe my opinions further below, with respect to the Examiner's comments and conclusions concerning the teachings and claimed inventions of the prior art.

Summary of the Inventions of the '882 Patent Application

5. The '882 patent application discloses a novel sterile calcium-free low bicarbonate dialysis concentrate composition for use in the preparation of a dialysis solution comprising sodium chloride (NaCl), magnesium chloride (MgCl2), and a concentration of sodium bicarbonate (NaHCO3) sufficiently low so as to allow preparation of a sterile dialysis solution having a bicarbonate concentration of 5-27.5 mmol/L.

6. As also described in the '882 patent application, the primary motivation for the development of the novel concentrate was to address problems known to be associated with buffers in general and there conversion to bicarbonate in the liver.

7. The solution to these issues involves the development of a novel dialysis concentrate having a bicarbonate level when diluted will prepare a dialysis solution in the range of 5 to 27.5 mmol/L and preferably 25.0 ± 2.5 mmol/L to reflect the "normal" level of bicarbonate of 25.0 mmol/L. This concentrate would be used in the preparation of a dialysis solution for patients who have achieved normal bicarbonate levels. If the bicarbonate level rises in the patient then bicarbonate would pass from the blood to the dialysate, and vice versa. The concentrate also provides, when diluted, the ability to compensate for the conversion of any weak acid, used as an anticoagulant in the dialysis process, to bicarbonate in the liver and assists in maintaining normal levels or as near to normal levels as possible.

8. Now shown to me and attached as **Exhibit B** to this my Declaration is U.S. Patent No. 5,945,449 to Purcell et al hereinafter referred to as Purcell. Claims 1, 9, 14, and 17 stand rejected

by the Examiner as being allegedly anticipated by our previous patent Purcell et al (US 5,945,449) from August 1999. I believe the examiner is of the mind that our old patent teaches a concentrate which is able to be simply diluted to achieve a sodium of 140. As found at column 6 of Purcell at line 10 it states that the bicarbonate concentrate may be used to produce a dialysis solution by mixing a sterile physiological acceptable diluent with a concentrate. Purcell goes on to specify which diluents are used. At line 20 in column 6 of Purcell the bicarbonate solution is generally prepared by mixing 80 ± 1 ml preferably 80 ml of concentrate with 1L of a sterile physiologically acceptable diluent. When diluted properly one is expected to end up with a solution measured in mmol/L of sodium of 140 ± 14, magnesium of 0.75 ± 0.07, chloride of 106.5 ± 10 and a bicarbonate of 35.0 ± 3.5 providing a 10 percent leeway for each component in either direction. I think Purcell was pretty specific saying that the concentrate should be diluted exactly as describe without going more than 10 percent in either direction. Of course, one could dilute Purcell further to get the bicarbonate concentration down below 30, however, all the other electrolytes would be diluted as well. So if we diluted the original NORMOCARB® 35 taught in Purcell to generate a bicarbonate of 25, the final solution would be 71.43 percent of the original which would dilute the sodium content from 140 to 100 and the chloride content from 106.5 to 76.1. The resulting dialysis solution would not be safe for use and will likely result in the quick death of a patient. Diluting the concentrate to achieve a dialysis solution in this manner is not acceptable. Each component must be carefully adjusted when the overall concentration is changed. I think the Examiner believes that all we have to do is add a little bit of fluid to the whole thing and we would just get a low bicarbonate in the range of 25.0 ± 2.5 mmol/L. Apparently the Examiner forgot that the sodium and chloride would change as well. A sodium of 100 in a proposed diluted Purcell solution to generate a bicarbonate of 25 as suggested by the Examiner is totally unacceptable. The Examiner has said that the Purcell concentrate is inherently capable of being so diluted. Certainly it is capable of being diluted but I hope that a physician who would try to carry out such a method would have their medical insurance paid in full as they would certainly lose it quickly when carrying out the Examiner's alleged procedure. Any practitioner doing so would be diluting the Purcell solution in this manner off label and I personally would not allow anybody who would do that to use our solution. Again the Examiner alleges that the bicarbonate level of Purcell's sterile calcium free concentrate may be used to prepare a solution going down to 5 mmol/L. However, reducing the bicarbonate amount in a dialysis solution based on the Purcell concentrate results in an absolutely ridiculous result for sodium of 20 which would be frankly toxic and hemolyze red cells on contact. The Examiner has ignored the statement in Purcell at column 6 line 20 that provides instructions to dilute 80 ml of

concentrate with 1 litre of a sterile physiologically acceptable diluent. It should be very clear from Purcell not to go beyond 10 percent variation which would be unacceptable. In conclusion the Examiner's allegations with respect to Purcell are without merit for the reasons I have expressed above.

9. Now shown to me and attached as **Exhibit C** to this my Declaration is PCT Patent Publication No. WO 96/01118 to Martis et al. hereinafter referred to as Martis. Martis and Lee Henderson have taught about peritoneal dialysis, which is a continuous form of dialysis. However it is a form of chronic dialysis performed at home for patients with chronic renal failure. It is rarely used in the intensive care setting. In this form of dialysis a dialysis solution is applied to the abdomen of the patient which dwells there for a period of time to allow diffusive exchange of toxins subsequently removed from the patient. As well, to improve the patient's acid-base balance bicarbonate equivalents from the solution diffuse into the patient. Traditionally peritoneal dialysis solution has always been based on lactate. Lactate that diffuses into the bloodstream is converted into bicarbonate by the liver. Thus every milliequivalent of lactate in the peritoneal dialysis solution is converted into bicarbonate after absorption. This is the reason that a peritoneal dialysis solution has higher levels of bicarbonate equivalents than a hemodialysis solution. A typical peritoneal dialysis lactate is 40 mEq/L.

10. Since the mid-1990s there has been interest in bicarbonate buffered peritoneal dialysis solutions. The reason that lactate or potentially other weak acids is chosen is that they do not interact with calcium or magnesium. Bicarbonate however when exposed in solution to calcium will precipitate as calcium carbonate or limestone. All attempts to create a peritoneal dialysis solution with bicarbonate uses split bank technologies to keep the calcium and bicarbonate separate. One other aspect that differentiates peritoneal dialysis solutions is a high concentration of dextrose. The dextrose acts as a high osmotic agent and its purpose is to remove water from the patient. Water flows down its osmotic gradient into the peritoneal dialysis solution from the patient achieving ultrafiltration. The solutions described by Martis all contain various concentrations of dextrose typical of peritoneal dialysis solutions.

11. The Martis paper describes a method of adding sodium bicarbonate at a minimum of 20 mmol per liter up to a maximum of 30 mmol/L. <u>It is critical to note that there is at least an additional 10 mEq of weak acid</u> that is added to the bicarbonate. Thus the solution described by Martis has no less than 30 mEq/L. of bicarbonate and equivalents.

12. There is clearly a difference between Martis and NORMOCARB® 25 with respect to equivalent bicarbonate levels. NORMOCARB® 25 is the trade name for the present invention. NORMOCARB® 25 has less than 30 mEq of bicarbonate with no additional weak acids. All the solutions described by Martis have a minimum of 30 mEq of bicarbonate equivalents or more. A physician might add a weak acid such as citrate to NORMOCARB® 25 and make a solution similar to Martis but doing so would be inconsistent with the intent of the invention. NORMOCARB® 25 is the first solution for acute dialysis that has a bicarbonate level and bicarbonate equivalents in the normal range of 25 mmol/L. Martis effectively does not address this!

13. The Martis paper also describes a function of bicarbonate to prevent the loss of the body's bicarbonate into solution down its concentration gradient by diffusion. It is unclear what is the intended significance of this statement. Regular peritoneal dialysis solution has a lactate of 40 and a bicarbonate of zero. The result is a loss of bicarbonate into solution by diffusion during the dwell of peritoneal dialysis solution in the abdomen. The solution described by Martis would prevent this happening as long as the body's bicarbonate level remained below the level of bicarbonate in Martis's solution of 20 to 30 mEq/L plus 10 to 20 mEq/L of bicarbonate equivalents provided by a weak acid. If the blood bicarbonate level rose above the level of total bicarbonate in the Martis solution then bicarbonate would start to be lost into the dialysate. Martis does not explain this event with evidence. As the lowest amount of bicarbonate equivalents in any of the solutions described by Martis is 30 mEq/L the patients may end up with a high level of bicarbonate when metabolizing the weak acid and the bicarbonate. NORMOCARB® 25 has a similar self adjusting effect for bicarbonate control. However there is no additional weak acid. The bicarbonate equivalents represent the total bicarbonate concentration of NORMOCARB® 25 namely 25 mEq ± 2.5. One of the general principles of dialysis is keeping blood levels of electrolytes within the normal ranges above-mentioned. With respect to acid-base balance, dialysis solutions have always had high levels of bicarbonate or bicarbonate equivalents as patients with kidney disease tend to have lower bicarbonate levels which is part of metabolic acidosis common with kidney disease. NORMOCARB® 25 was designed for patient's who have reached normal levels of bicarbonate. The principle of maintaining a bicarbonate level around the normal physiologic level of 25 mmol/L is an important principle. If the body's bicarbonate level rises above 25 mmol/L, bicarbonate will diffuse into dialysate. If the body's bicarbonate level drifts below 25 mmol/L, bicarbonate will be added to it from the dialysate. This principle is no different for bicarbonate as it is for sodium,

chloride or magnesium, the other components of NORMOCARB® 25. During dialysis if the patient's sodium level is above 140, sodium ions will be lost into the dialysate until the level falls to 140. If the sodium level is below 140 sodium ions will enter the bloodstream from the dialysate to rectify the levels. What is novel about NORMOCARB® 25 is that it is the first dialysis solution to attempt to achieve a normal level of bicarbonate in continuous renal replacement therapy using a "normal" level of bicarbonate in the dialysate.

14. Martis teaches bicarbonate concentration of about 20 to 30 mM equivalent which in my opinion makes the Examiner think that Martis is talking about the same thing as the present invention. However, Martis also teaches the addition of 10 - 20 mM equivalence per litre of a weak acid. Now that weak acid may consist of lactate, pyruvate, citrate, and isocitrate, or any other acceptable weak acid which will be converted to bicarbonate in the liver.

15. Claim 15 of Martis on line 20 on page 15, includes the step of administering to the patient a weak acid that is present in the solution in an amount that offsets the daily hydrogen production of approximately 1mEq/kg/day. This teaching in fact is an admission by Martis that the purpose of the weak acid is to be metabolized into something that offsets that daily production, i.e. it gets metabolized to bicarbonate. What Martis is therefore describing is a solution that has 20 to 30 mM of bicarbonate but also has 10 to 20 mM of weak acids such as lactate that gets converted directly into bicarbonate. Peritoneal dialysis solution typically has only lactate in the solution. This is a bicarbonate equivalent and lactate is converted 1 to 1 by the liver into bicarbonate and this is why peritoneal dialyses solution with lactate can provide resolution of metabolic acidosis. The lactate is a bicarbonate equivalent. In Martis the weak acid also is a bicarbonate equivalent. In fact, if citrate is used each citrate molecule gets converted into 3 molecules of bicarbonate so that 10 to 20 mM equivalents of citrate actually gets turned into 30 to 60 mM equivalents of bicarbonate. The lowest bicarbonate that Martis talks about would be a combination of 20 mM of sodium bicarbonate plus 10 mM of a weak acid such as lactate which only yields 1 bicarbonate equivalent per molecule of lactate which would give a total of 30 mM of bicarbonate equivalents. Thus the lowest bicarbonate equivalent in Martis's patent is 30 mmol/L and the current invention teaches 25.0 ± 2.5 mmol/L. The Examiner then purports that one skilled in the art would use the Martis dialysis solution in combination with the teachings of Purcell to render our current patent claims allegedly obvious. Again, neither Purcell nor Martis teach a bicarbonate level or bicarbonate equivalents below 30. The minimum Martis and Purcell bicarbonate equivalent level

is 30 and 31.5 respectively but well above Applicant's teaching. In fact neither party appreciated the benefits available in so doing.

One concern I have about Martis' disclosure is the calcium level of the solution has a range from 0.0 to 4.0. All of the examples that Martis gives are with a calcium of 3.5 mEq/L. This is the standard calcium concentration in peritoneal dialysis solution. Theoretically a peritoneal dialysis solution could have a calcium level of 0. I am unaware of any commercially available solutions that have a calcium of 0. As peritoneal dialysis solution is typically used for chronic dialysis, calcium in the solution of 0 mEq/L would lead to chronic lose of calcium and would need regular supplementation. A solution with 0 calcium however would not lead to any precipitation with bicarbonate. Adding any calcium to the peritoneal dialysis solution described by Martis that also contains bicarbonate to minimum of 20 mmol/L would lead to precipitation between calcium and bicarbonate. This would particularly occur in the sterilization phase which generally involves heat. The only situation covered by Martis in which this would not occur is if the weak acid was citrate in which case citrate would chelate the calcium and likely prevent precipitation with bicarbonate. This situation is not covered in the disclosure by Martis. Also a peritoneal dialysis solution containing citrate would not deliver calcium to the patient but might also chelate the patient's calcium leading to low calcium levels in the patient and clinical problems due to the low calcium levels. Martis does not present evidence that they have been able to create a solution that has both bicarbonate and calcium that does not precipitate or that they have clinical evidence that a solution with no calcium would be safe.

16. Now shown to me and attached as **Exhibit D** to this my Declaration is previously cited Chemical Abstracts 124:325351 to Koo et al. hereinafter referred to as Koo. The Koo disclosure describes a calcium-free dialysate for dialyzing patients who are hypercalcemic because of malignancy. These are calcium free dialysates. However, Koo is used for intermittent hemodialysis. Koo's dialysate is not sterile because he is using concentrates with a classic intermittent dialysis machine. The Examiner alleges that the sterile feature would have been necessarily present in a dialysate for hemodialysis. This is not the case. Hemodialysis typically does not use sterile dialyzing. There is nothing in Koo to suggest that he did. Koo does use a concentrate to make up their dialysis solution but it is a standard commercially available calcium free dialysate that was known. The Examiner alleges that we did not provide distinguishing language in Claim 14 since allegedly no specific dilution factor was claimed. I submit that one skilled in the art would understand that 80 ml of concentrate is to be diluted with 1L of sterile

diluent and we have made it clear in the disclosure that the solution is to be diluted appropriately within 10 percent variation.

17. The Examiner alleges that Claims 1, 9-10, 14 and 17 are rejected as being unpatentable over Koo. The Examiner alleges that the sterile feature is present. This is not the case. It is not a simple matter to sterilize a bicarbonate concentrate. It can not be heat sterilized when magnesium is present. We must consider this issue as well or else the magnesium will precipitate into insoluble crystals. When providing continuous renal replacement therapy as we do, it is necessary to provide sterile dialysate, but that is not at all what Koo teaches. He only was addressing intermittent hemodialysis. Koo did not refer to any specific dilution factors. The present invention teaches dilution of the dialysis solution from concentrate of 80 ml with 1000 mls of sterile water to make 1,080 mls of dialysis solution just as in Purcell. Perhaps this is why the Examiner thinks one can just dilute NORMOCARB® 35 to any degree to yield any alleged proper bicarbonate level. Again the Examiner infers preparation of a concentrate then diluting that concentrate to the component concentration desired because concentrates generally provide the advantage of storage stability and convenience. We take the electrolyte components for the concentrate which are calcium-free but do contain magnesium and sterilized and packaged it for convenience. That was not obvious in 1999 and it is not obvious today because no one else has done this. The Examiner continues on page 9 & 10 with respect to Koo that doing so is obvious. There are commercially available calcium free dialysis solutions which are not sterile. Dialysis solutions are packaged in two separate containers; there is a bicarbonate container with a concentrate and an acid container that contains the magnesium and additional sodium. These two containers are attached to a dialysis machine <u>in a non sterile manner</u>. The solutions are drawn up inside the machine. They are proportioned with non sterile but clean reverse osmosis water. They are prepared by the dialysis machine into a dialysate which according to the instructions of Koo is a calcium-free dialysate. This is dependent on dual proportioning with a proper safety mechanism to provide a dialysate of exactly the right concentration of sodium and bicarbonate. The simple dilution of the concentrate to yield a dialysis solution in a big jug and preparing it properly is not obvious or easy. Our solution when diluted appropriately makes a dialysate of exactly the correct concentration of sodium, bicarbonate, chloride and magnesium which is also sterile. The teachings of Koo does not make this obvious in my opinion for the reasons set out above.

18. The Examiner in his Action of August 11, 2005 has stated that the sterile feature would have been necessarily present in a dialysate for hemodialysis. I disagree with this statement since these compositions are not sterile. One of the problems in sterilizing dialysate is by adding heat the ion concentration is altered. The dialysis concentrate of the present invention is in fact sterilized by cold filtering. Further the Examiner has alleged that the Koo reference includes the exact composition of ingredients of the present invention and alleges that the same properties must necessarily be present thus incorrectly concluding that the claim is somehow anticipated.

19. The Examiner alleges that one skilled in the art would have been motivated to provide a sterile dialysis concentrate or solution in order to ensure patient safety; however in carrying out the instructions of the Examiner to dilute the concentrate beyond the recommended levels one skilled in the art is placing the patient at considerable risk. The Examiner in preparing his obviousness rejection has relied considerably on the ability of one skilled in the art to choose sodium chloride, magnesium chloride and sodium bicarbonate and prepare a dialysate with the required balance of ions. The Examiner then further alleges that Koo teaches a concentration of 30 mmol/L. However he also suggests that one skilled in the art would have been motivated to modify the bicarbonate concentration of Koo and still expect the successful treatment of hypercalcemia. The Examiner refers to the term "slightly" but this is not correct since the modification and the motivation to do so is clearly lacking in the art. Why would one skilled in the art, namely a Nephrologist, modify the concentration "slightly" with the full knowledge that these ions are critical to individual patient health and therefore must be carefully balanced in the dialysis solution. To provide a "similar" ion content and make-up is unacceptable. The criticality of getting the ion concentration correct is established with the present invention. Further by making the alleged "slight" modifications for bicarbonate content, the other ions are thrown out of balance. A physician would never use such a dialysate.

20. The Koo reference does not teach low bicarbonate levels but only that of 30 mmol/L. Applicant further submits that Koo only discloses a composition containing sodium 135 mmol/L, potassium 2.5 mmol/L, chloride 108 mmol/L, magnesium 0.75 mmol/L and <u>bicarbonate 30 mmol/L</u>. The claims have now been limited to bicarbonate of 5 to 27.5 which clearly is not taught in Koo.

21. I submit that the essence of the present invention is particularly summarized at page 7, lines 16-30,

> "... Usage of a low bicarbonate dialysate solution of the invention takes into account the bicarbonate derived from citrate, and as a result the total effective bicarbonate concentration is accounted for and effectively controlled. Thus, metabolic complications are effectively minimized. The low bicarbonate sterile solution of the invention typically contains a bicarbonate concentration within the range of 5-30 mmol/L, preferably between 20-30 mmol/L, and more preferably 25 ± 2.5 mmol/L. The solutions with bicarbonate concentrations below 25 mmol/L may have sodium citrate added to them up to 20 mmol/L to act as an anticoagulant. *(emphasis added)*
>
> The benefit of such a low concentration of bicarbonate as 25 mmol/L is that if the patients bicarbonate level drops below this, bicarbonate diffuses from the dialysate across the semipermeable membrane to the patient correcting the problem. If there is an excess of bicarbonate in the blood (metabolic alkalosis) then bicarbonate will diffuse out into the dialysate effluent and be removed returning the patient toward normal."

22. I conclude that Koo does not teach a solution containing less than 30 mmol/L of bicarbonate and the ion balancing feature in the present invention above-mentioned will not take place. There is no indication or motivation in Koo of addressing the problem identified in Applicant's disclosure, or any reasoning for selecting low levels of bicarbonate in a dialysis solution. The invention in Koo would not render the present invention obvious to a person skilled in the art, based on his common general knowledge, since it does not teach or even suggest an effective level of bicarbonate below 30 mmol/L, nor motivate one skilled in the art to do so.

23. None of the prior art in my opinion would lead a person skilled in the art to prepare and use a solution containing less than 30 mmol/L of bicarbonate. There is no teaching in Koo of the problem I am addressing nor any reason for selecting low levels of bicarbonate in their dialysis solution.

24. The teachings of Koo therefore would not render the present invention obvious to a person skilled in the art, based on his common general knowledge, since Koo does not teach or even infer a low effective level of bicarbonate below 30 mmol/L nor motivate one skilled in the art to do so. Considering that Koo does not teach in this direction, how could any combination of references result in the amended claim set.

25. Now shown to me and attached as **Exhibit E** to this my Declaration is U.S. Patent No. 6,492,336 to Mahiout hereinafter referred to as Mahiout. Mahiout teaches a peritoneal dialysis solution that has calcium of 1 to 5 mEq/L as well as 25 to 40 mM equivalence of anions which

could include bicarbonate. The peritoneal dialysis solution of Mahiout includes "at least one sugar derivate" as an essential element of that invention. The "at least one sugar derivative" is present for the removal of water and solutes from a patient by peritoneal dialysis (see column 3, lines 40-43). At least one sugar derivative is not present nor is it intended to be present in the present invention. But "at least one sugar derivative" is an essential element of Mahiout's invention and thus a person skilled in the art could not conceivably derive a composition not containing this essential element from the teachings of Mahiout. Clearly Mahiout does not teach a calcium free low bicarbonate dialysis concentrate for use in preparation of a dialysis solution. Every one of the Examples 1-16 of Mahiout include calcium.

26. The present invention is clearly novel and unobvious in light of Mahiout for the following reasons.

Mahiout describes a dialysis fluid containing:

from 125 to 140 mEq/L of sodium;
from 90 to 125 mEq/L of chloride;
from 1 to 5 mEq/L of calcium; (emphasis added)
from 0.2 to 5 mEq/L of magnesium;
and from 25 to 40 mEq/L of a buffering anion selected from the group consisting of lactate, pyruvate and bicarbonate.

Therefore the Mahiout composition cannot be considered as "calcium free". Further, no discussion of low bicarbonate levels is taught nor the reasoning for doing so.

I also submit that in the description of Mahiout an essential element of the invention is the presence of "at least one sugar derivative" which derivative is described at column 3, lines 43-59 of that patent.

27. The objects and teachings of Mahiout are clearly not related to the present invention. Mahiout teaches a glucose free hydrogenated oligosaccharide solution having no effect on cell function during peritoneal dialysis. Further, one will note upon review of the examples provided in Mahiout, more specifically examples 2, 6, 10, and 14, it is discussed that the amount of bicarbonate is 2.94 g/l which works out to 35 mmol/L. Also in examples 4, 8, 12, and 16 it is

discussed that the amount of bicarbonate is 2.52 g/l which works out to 30 mmol/L. None of the examples in Mahiout discuss or even suggest a calcium-free dialysis solution with 27.5 mmol/L or less of bicarbonate as is now claimed in the present application. In view of the present amendments to the claims it is submitted that the Examiner's rejection has been traversed in that Mahiout does not teach a calcium free, low bicarbonate dialysis solution. There is no discussion in Mahiout to even motivate one skilled in the art in that direction.

28. Thus, it is my opinion that none of Purcell, Martis, Koo or Mahiout either alone or in any combinations thereof teach towards or disclose the claimed inventions as amended in the present submission. As a result, I disagree with the statements made and conclusions reached by the Examiner with respect to these points as described above.

29. I solemnly declare and affirm further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereof.

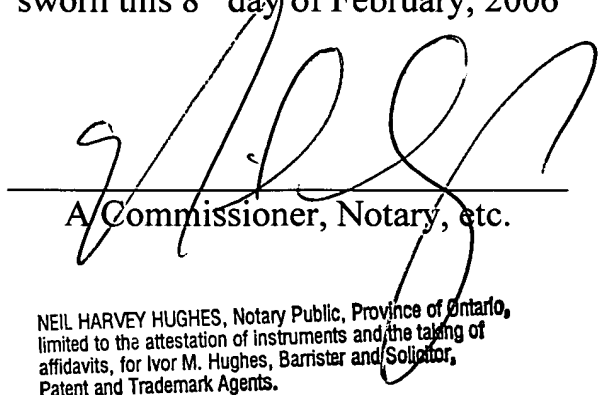
AFFIRMED before me)
at the Town of Markham)
in the Province of Ontario, Canada)
this 8th day of February, 2006)

Commissioner, Notary Public
for taking Oaths

NEIL HARVEY HUGHES, Notary Public, Province of Ontario,
limited to the attestation of instruments and the taking of
affidavits, for Ivor M. Hughes, Barrister and Solicitor,
Patent and Trademark Agents.
Expires March 30, 2007.

Dr. Sheldon William Tobe, M.D.
Staff Nephrologist, Sunnybrook Health Science Centre
Associate Professor of Medicine, University of Toronto

This is EXHIBIT A referred to in the
Declaration of Sheldon William Tobe, M.D.
sworn this 8th day of February, 2006



A Commissioner, Notary, etc.

NEIL HARVEY HUGHES, Notary Public, Province of Ontario,
limited to the attestation of instruments and the taking of
affidavits, for Ivor M. Hughes, Barrister and Solicitor,
Patent and Trademark Agents.
Expires March 30, 2007.

CURRICULUM VITAE
Sheldon William Tobe

Date Prepared: February 7, 2006

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BIOGRAPHICAL INFORMATION

Degrees

B.Sc.: June, 1982, University of Toronto, B.Sc. Honours Biochemistry.

M.D: June, 1985, University of Calgary, M.D.

Additional Courses

1985 Clinical Biochemistry, University of Calgary
1990 Clinical Epidemiology, University of Toronto

Employment:

1985-1986.	Comprehensive Intern, Internal Medicine, Sunnybrook Health Science Centre, University of Toronto.
1987-1988	Resident in Internal Medicine (PGY 2), Mount Sinai Hospital, University of Toronto.
1988-1989	Resident in Internal Medicine (PGY 3), The Toronto Hospital, General Division, University of Toronto.
1989-1990	Resident in Nephrology, The Toronto Hospital, University of Toronto.
1990-1993	MRC Research Fellow, Nephrology, The Toronto Hospital, University of Toronto.
1993 - 2005	Assistant Professor of Medicine, University of Toronto, Staff Nephrologist, Sunnybrook Health Science Centre, Toronto, Ontario. University Job Description: Clinical-Investigator.
2005 to present	Associate Professor of Medicine, University of Toronto, Staff Nephrologist, Sunnybrook Health Science Centre, Toronto, Ontario.

Practice Experience

General Practice	July, 1986 - June, 1987
General Internal Medicine	July 1990-1993 Locum Tenens Specialty
July 1993 to present	Staff Nephrologist, Sunnybrook and Women's College Health Science Centre

Honours and Academic Awards

1980-82	Faculty Scholar, University of Toronto
1982	B.Sc. with Distinction 1982
1982-85	University of Calgary. Nat Christie Award, Tuition Scholarship.
1990-93	MRC Fellowship. Nephrology. Dr. K. Skorecki, Supervisor.
1992	First Place: The Toronto Hospital Research Competition, Clinical research.
1993	Canadian Society of Nephrology - Upjohn Trainee Award
1996	Sunnybrook Health Science Centre Department of Medicine Young Clinician-Teacher Award, 1996
2002	Sunnybrook and Women's College Health Science Centre, Department of Medicine Inpatient Teaching Award

Certification

MD	University of Calgary: June 5, 1985
LMCC	The Medical Council of Canada: June 17, 1986
National Boards	National Board of Medical Examiners Parts 1,2,3:NBME No. 328871
General Licence	The College of Physicians and Surgeons, Ontario: No. 55894, 1986
ABIM	American Board of Internal Medicine: January, 1990.
ACP Member	American College of Physicians. No 040625: January, 1990.
FRCPC	Internal Medicine. Fellow of the Royal College of Physicians of Canada: June, 1990. ID # 390895
FRCPC	Nephrology. Fellow of the Royal College of Physicians of Canada: November, 1991.
ABIM	American Board of Internal Medicine, Board Certified in Nephrology: November, 1992.
ASH Specialists	The American Society of Hypertension. February 2000. C0042.

Professional Affiliations and Activities

Alumni and Friends of the Medical Research Council of Canada (MRCC)
American College of Physicians
American Heart Association
American Society of Hypertension
American Society of Nephrology
Canadian Diabetes Association
Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada – Management of Nephropathy
Canadian Hypertension Society
Canadian Hypertension Education Program: Evidence-based Task Force
Guidelines Committee, 1999 to present – Renal and Renal Vascular and Diabetes subgroups
Canadian Hypertension Society Board Member 2003 to present
Canadian Society of Nephrology
Canadian Society of Nephrology Education Committee 1998 - 2005
Council for High Blood Pressure Research, American Heart Association
Drug Utilization Advisory Committee (MOHLTC)
International Society of Nephrology
Kidney Foundation of Canada-Central Ontario Branch Board of Directors – Medical Director (1999-02)
Kidney Foundation of Canada-Ontario Medical Advisory Committee – Executive Member (1999-03)
National Aboriginal Diabetes Association (2004 to present)
Ontario Medical Association – the physician leader (1999 to 2004)
Royal College of Physicians and Surgeons of Canada (Fellow)

Journal Reviewer

American Journal of Kidney Diseases
American Society of Artificial Internal Organs
American Journal of Hypertension
Blood Pressure Monitoring
Canadian Journal of Cardiology
Canadian Medical Association Journal
Circulation
Kidney International
Hepatology
The Journal of Cardiac Surgery
The Journal of Critical Care
The Journal of Rheumatology
Nephron

University Committees

1994 to present	Toronto Regional Dialysis Committee
1996-98	Department of Medicine: Continuing Medical Education Committee
1998	Masters Thesis Review Committee – Dr. Vanita Jassal
1996-2000	Post Graduate Education Committee, Division of Nephrology
1999 to 2003	Division of Nephrology Executive Committee
2005 to present	University of Toronto Clinical Research Committee

Hospital and Other Administrative Committees

1994 - 2003	Sunnybrook Trust for Medical Research, Grant Review Committee
1995–2000	Post Graduate Education Committee (Sunnybrook)
1995–1999	Electronic Patient Record Committee (Sunnybrook)
1995	Chair, General Internal Medicine Core Review
1997–1997	Ontario Association of Nephrologists Executive, Metro Toronto Liaison Member
1997–1999	Ontario Association of Nephrologists Executive, Relative Value Service Representative
1999 – 2003	Acting Division Director Division of Nephrology Sunnybrook and Women's College Health Science Centre
1997 to present	Sunnybrook and Women's College Research Committee
2005 – present	Director, SWCHSC Department of Medicine Research Committee
2000 to 2005	Canadian Society of Nephrology Education Committee
2002 to present	Sunnybrook and Women's College Residency Training Committee
2002–2003	Sunnybrook Hospital/University of Toronto Clinic (SHUTC) Board of Directors
2003 to present	Canadian Institute of Health Research National Consultation Committee
2003 to present	Ontario Ministry of Health Clinical Diabetes Sub-Committee
2005	Heart and Stroke Foundation: HBP AIM provider Management Advisory Group Mentor

ACADEMIC HISTORY

Research Awards – Peer Reviewed

1994-96 High Efficiency Bicarbonate Peritoneal Dialysis, Bicarbonate Unit Dose Dialysate for Slow Continuous Haemodialysis and Dialysis During Cardiac Bypass. Patent application pending. Funded by Sunnybrook Trust for Research. Award $23,000.
Role: Principal Investigator.

1996-97 MRC/PMAC Operating Grant. Erythropoietin, Time Dependent Activity in Renal Failure Patients. Award $142,456.
Role: Co-Investigator with Dr. G. Bjarnason, Toronto Bayview Cancer Clinic.

1996-98 The Heart and Stroke Foundation. Hypertension, Job and Marital Strain and Left Ventricular Mass Index: A Three Year Follow-up. Award $44,000.
Role: Co-Principal Investigator with Dr. B. Baker, Dept of Psychiatry, The Toronto Hospital.

1997-99 PSI. Low Dose Warfarin for the Prevention of Polytetrafluoroethylene (PTFE) Graft Thrombosis in Hemodialysis Patients. Award $66,700.
Role: Local PI of Multicentre study, Dr. A. Ingram, PI, McMaster University

1998 -99 MRC. A Placebo-Controlled Study of Folic Acid Adherence in Hemodialysis Patients. Award $30,000.
Role: Senior Investigator, Karin Helmers PI

Research Awards – Peer Reviewed (Con't)

2000 – 2001 PSI. HIPPO Study. To determine if the incidence of hemodialysis catheter related infections is significantly reduced in individuals on hemodialysis when topical Polysporin Triple compound is applied to their catheter insertion site compared to the application of placebo ointment.
Role: Site PI, Charmaine Lok MD, Toronto Hospital Co-investigator

2001-3 Heart & Stroke Foundation of Ontario. Double Exposure Study of Stress Effects on Hypertension. Two year study, $160,345 - a third year renewable.
Role: Principal Investigator. Co-investigator: Brian Baker, U of Toronto

2001-4 CIHR University-Industry Program. DREAM 3: Diabetes Risk Evaluation & Microalbuminuria in Saskatchewan First Nations Peoples. Award $235,300
Role: Principal Investigator. Collaborators: Dr. Georg Pylypchuk, U of Saskatchewan

2003-4 Heart and Stroke Foundation of Ontario. Double Exposure Stress Effects on Hypertension. One year renewal. Award $73,075.
Role: Principal Investigator. Co-investigator: Dr. Brian Baker, UHN

2005 – 2007 Physicians' Services Incorporated Foundation (PSI)
Renal Atherosclertoic Revascularization Evaluation (RAVE) Study
Award $88,000. Role: Prinicpal Investigator.

Research Awards – Non Peer-Reviewed

1994 Ortho Biotech. Time Dependent Action of Erythropoeitin in Haemodialysis and Effect on Blood Pressure. Award $53,000.
Role: Co-Investigator with Dr. G. Bjarnason, Toronto Bayview Cancer Clinic.

1996 Scios Nova Inc. A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Clinical Trial to Evaluate the Safety and Efficacy of AURICULIN Anaritide in the Treatment of Oliguric Acute Tubular Necrosis. Award $44,871.
Role: Co-investigator with Dr. Terry Smith, Sunnybrook Hospital.

1997-2002 Searle Canada, Inc. Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE). Award $32,500
Role: Local PI of Multinational study. Dr. H. Black, PI, Chicago (Rush Presbyterian Health Science Centre)

1998 Alteon Inc. Ramsey, NJ. A Placebo-Controlled Safety and Efficacy Study of Pimagedine in Diabetic Patients with End-Stage Renal Disease on Hemodialysis. Award $126,320
Role: Local PI of Multinational Study

Research Awards – Investigator Initiated (Principal Investigator)

1996-98 Bristol Myers Squibb. Microalbuminuria: Nephropathy Impact of Drug Dosing with Monopril. Award $90,000.

Research Awards – Investigator Initiated (Con't)

1997 Ortho Biotech. A Study to Determine the Impact of Hemoglobin Maintenance and Other Interventional Strategies to Prevent or Delay the Progression of Left Ventricular Mass Growth in Patients with Early Renal Insufficiency (ERI). Award $16,500. Dr. A. Levin, PI. Local PI of Multicentre Canadian study.

1998 Hemosol Inc. Can a Hemoglobin Based Oxygen Carrier (Hemolink) Speed Red Cell Formation in Iron Replete Hemodialysis Subjects. Award $36,500.

1999 Hemosol Inc. Can a Hemoglobin Based Oxygen Carrier (Hemolink) Improve Tissue Oxygenation in Chronic Hemodialysis Subjects with Peripheral Vascular Disease. Award $16,500. Dr. S Tobe, Dr. L Carmichael.

1999-05 Novartis Pharma Inc. VALUE Study. A prospective, multinational, multicentre, double blind, randomized, active-controlled trial in patients with essential hypertension to compare the effect of Valsartan 80 and 160 mg. With or without the addition of hydrochlorothiazide, once daily to that of amlodipine 5 and 10 mg. once daily, with or without the addition of hydrochlorothiazide, on cardiovascular morbidity and mortality. Award $51,000.

1999-05 Searle. EPLERENONE LONG-TERM OPEN-LABEL Study. The objective of this study is to assess the long-term safety and efficacy of eplerenone as determined by adverse events, clinical laboratory values, and withdrawals for uncontrolled blood pressure. Award $88,200.00

2000-01 Advanced Dialysis Methods. VIBRATED PERITONEAL DIALYSIS. Award $39,364.00.

2000-01 Janssen-Ortho. Double Blind Study To Assess The Impact Of Normalization Of Hemoglobin Compared To Partial Correction Of Hemoglobin With Eprex On Left Ventricular Structure In Early Hemodialysis Patients. Award $99,100.00

2000-01 Bayer. CHORUS Study. A randomized, double-blind, parallel group evaluation of usual care plus Cerivastatin 0.4 mg once daily compared with usual care(placebo) alone in patient with End Stage Renal Disease(ESRD) New to Hemodialysis:Cerivastatin Heart Outcomes in Renal Disease:Understanding Survival. Award $103,870.00

2000-01 Bayer. CAPSIZE Study. The objective of this study is to examine the progression of carotid atherosclerosis using a simple, non-invasive ultrasound technique, in patients treated in a two-year randomized , placebo-controlled, double-blind clinical trial of cerivastatin in hemodialysis patients. Award $ 19,450.00

2004 Pfizer Pharmaceuticals. DREAM 3 (Diabetes Risk Evaluation and Microalbuminuria) Longitudinal Study. Award $59,480

PUBLICATIONS

PUBLICATIONS AND PAPERS – Refereed

1. Carlisle EJ, Donnelly SM, Vasuvattakul S, Kamel KS, **Tobe S**, Halperin ML. Glue-sniffing and distal renal tubular acidosis: sticking to the facts. [Review] [43 refs]. Journal of the *American Society of Nephrology* 1991;**1**:1019-27.
(Collaborator: 20%)

2. Morali GA, Floras JS, Legault L, **Tobe S**, Skorecki KL, Blendis LM. Muscle sympathetic nerve activity and renal responsiveness to atrial natriuretic factor during the development of hepatic ascites. *American Journal of Medicine* 1991;**91**:383-92.
(Collaborator: 20%)

3. **Tobe S**, Chu MG, Bargman JM. Characterization of peritoneal transport in patients with failed renal allografts receiving CAPD. *Advances in Peritoneal Dialysis* 1991;**7**:39-43.
(Collaborator: 20%)

4. Gallicano KD, **Tobe S,** Sahai J, McGilveray IJ, Cameron DW, Kriger F et al. Pharmacokinetics of single and chronic dose zidovudine in two HIV positive patients undergoing continuous ambulatory peritoneal dialysis (CAPD). *Journal of Acquired Immune Deficiency Syndromes* 1992;**5**:242-50.
(Co-principal author: 60%)

5. Morali GA, **Tobe SW**, Skorecki KL, Blendis LM. Refractory ascites: modulation of atrial natriuretic factor unresponsiveness by mannitol. *Hepatology* 1992;**16**:42-8.
(Co-principal author: 60%)

6. Morali GA, Sniderman KW, Deitel KM, **Tobe S**, Witt-Sullivan H, Simon M et al. Is sinusoidal portal hypertension a necessary factor for the development of hepatic ascites? *Journal of Hepatology* 1992;**16**:249-50.
(Collaborator: 20%)

7. **Tobe SW**, Morali GA, Greig PD, Logan A, Blendis LM. Peritoneovenous shunting restores atrial natriuretic factor responsiveness in refractory hepatic ascites. *Gastroenterology* 1993;**105**:202-7.
(Senior responsible/Principal Author: 90%)

8. **Tobe SW**, Blendis LM, Morali GA, Warner LC, Logan AG, Skorecki KL. Angiotensin II modulates atrial natriuretic factor-induced natriuresis in cirrhosis with ascites. *American Journal of Kidney Diseases* 1993;**21**:472-9.
(Senior responsible/Principal Author: 90%)

9. Wong F, **Tobe S**, Legault L, Logan AG, Skorecki K, Blendis LM. Refractory ascites in cirrhosis: roles of volume expansion and plasma atrial natriuretic factor level elevation. *Hepatology* 1993;**18**:519-28.
(Co-principal author: 60%)

10. Wong F, Liu P, **Tobe S**, Morali G, Blendis L. Central blood volume in cirrhosis: measurement with radionuclide angiography. [see comments.]. Hepatology 1994;**19**:312-21.
(Collaborator: 20%)

11. **Tobe SW**, Siu LL, Jamal SA, Skorecki KL, Murphy GF, Warner E. Vinblastine and erythromycin: an unrecognized serious drug interaction. [see comments.]. *Cancer Chemotherapy & Pharmacology* 1995;**35**:188-90.
(Senior responsible/Principal Author: 90%)

12. **Tobe SW**, Noble-Topham SE, Andrulis IL, Hartwick RW, Skorecki KL, Warner E. Expression of the multiple drug resistance gene in human renal cell carcinoma depends on tumor histology, grade, and stage. *Clinical Cancer Research* 1995;**1**:1611-5.
(Senior responsible/Principal Author: 90%)

13. Warner E, **Tobe SW**, Andrulis IL, Pei Y, Trachtenberg J, Skorecki KL. Phase I-II study of vinblastine and oral cyclosporin A in metastatic renal cell carcinoma. *American Journal of Clinical Oncology* 1995;**18**:251-6. (Co-principal author: 60%)

14. Manuel A, Gray B, Coulis N, Brunier G, Desson F, **Tobe SW**, Paton M. Designing dialysis prescriptions. *Advances in Peritoneal Dialysis* 1996;**12**:136-42.
(Collaborator: 20%)

15. **Tobe SW**, Senn JS. Foregoing renal dialysis: a case study and review of ethical issues. The End-Stage Renal Disease Group. [Review] [33 refs]. *American Journal of Kidney Diseases* 1996;**28**:147-53.
(Senior responsible/Principal Author: 90%)

16. Bhaskaran S, **Tobe S**, Saiphoo C, Moldoveanu A, Raj DS, Manuel MA. Blood urea levels 30 minutes before the end of dialysis are equivalent to equilibrated blood urea. *ASAIO Journal* 1997;**43**:M759-M762.
(Co-principal author: 60%)

17. Raj DS, **Tobe S**, Saiphoo C, Manuel MA. Quantitating dialysis using two dialysate samples: a simple, practical and accurate approach for evaluating urea kinetics. *International Journal of Artificial Organs* 1997;**20**:422-7.
(Co-principal author: 60%)

18. Baker B, O'Kelly B, Szalai JP, Katic M, McKessock D, **Tobe SW**, Ogilvie R. Determinants of left ventricular mass in early hypertension. *American Journal of Hypertension* 1998;**11**:1248-51.
(Collaborator: 20%)

19. Raj DS, **Tobe SW,** Saiphoo CS, Manuel MA. Mass balance index: an index for adequacy of dialysis and nutrition. *International Journal of Artificial Organs* 1998;**21**:328-34.
(Co-principal author: 60%)

20. Baker B, Helmers K, O'Kelly B, Sakinofsky I, Abelsohn A, **Tobe S**. Marital cohesion and ambulatory blood pressure in early hypertension. *American Journal of Hypertension* 1999;**12**:227-30.
(Senior responsible author: 90%)

21. Levin A, Thompson CR, Ethier J, Carlisle EJ, **Tobe S**, Mendelssohn D *et al.* Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *American Journal of Kidney Diseases [Online]* 1999;**34**:125-34.
(Collaborator: 20%)

22. **Tobe SW**, Murphy PM, Goldberg P, Harwood S, McLean R, Christakos G *et al.* A new sterile bicarbonate dialysis solution for use during cardiopulmonary bypass. *ASAIO Journal* 1999;**45**:157-9.
(Senior Responsible author/principal author: 90%

23. Zimmerman D, Cotman P, Ting R, Karanicolas S, **Tobe SW**. Continuous veno-venous haemodialysis with a novel bicarbonate dialysis solution: prospective cross-over comparison with a lactate buffered solution. *Nephrology Dialysis Transplantation* 1999;**14**:2387-91.
(Senior responsible author: 90%)

24. Baker B, Paquette M, Szalai JP, Driver H, Perger T, **Tobe SW**, Helmers K. The influence of marital adjustment on 3-year left ventricular mass and ambulatory blood pressure in mild hypertension. *Archives of Internal Medicine* 2000;**160**:3453-8.
(Collaborator: 20%)

25. Helmers KF, Baker B, O'Kelly B, **Tobe S**. Anger expression, gender, and ambulatory blood pressure in mild, unmedicated adults with hypertension. *Annals of Behavioral Medicine* 2000;**22**:60-4.
(Senior responsible author:90%)

26. Tannenbaum H, **Tobe S** et al. An evidence based approach to prescribing NSAIDs in the treatment of osteoarthritis and rheumatoid arthritis: the second canadian consensus conference. *Cdn J of Clin Pharm.* 2000; 7(A):4-16.
(Collaborator: 20%)

27. Abrahamov D, Tamariz M, Fremes S, **Tobe S**, Christakis G, Guru V *et al.* Renal dysfunction after cardiac surgery. *Canadian Journal of Cardiology* 2001;**17**:565-70.
(Collaborator: 20%)

28. Epstein M,.**Tobe S.** What is the optimal strategy to intensify blood pressure control and prevent progression of renal failure?. [Review] [45 refs]. *Current Hypertension Reports* 2001;**3**:422-8.
(Co-principal author:60%)

29. Leung GM, Redelmeier DA, Szalai JP, Boyle E, Hilditch JR, **Tobe SW.** Microalbuminuria screening for patients having type 2 diabetes mellitus: who wants to participate? *Clinical & Investigative Medicine - Medecine Clinique et Experimentale* 2001;**24**:37-43.
(Senior responsible author: 90%)

30. Levin A, Djurdjev O, Barrett B, Burgess E, Carlisle E, **Tobe SW**, Ethier J. Cardiovascular disease in patients with chronic kidney disease: getting to the heart of the matter. *American Journal of Kidney Diseases [Online]* 2001;38:1398-407.
(Collaborator: 20%)

31. McAlister FA, Levine M, Zarnke KB, Campbell N, Lewanczuk R, **Tobe SW**, Leenen F. The 2000 Canadian recommendations for the management of hypertension: Part one--therapy. *Canadian Journal of Cardiology* 2001;17:543-59.
(Collaborator: 20%)

32. Zarnke KB, Levine M, McAlister FA, Campbell NR, Myers MG, **Tobe SW**, McKay DW. The 2000 Canadian recommendations for the management of hypertension: part two--diagnosis and assessment of people with high blood pressure. [Review] [84 refs]. *Canadian Journal of Cardiology* 2001;**17**:1249-63.
(Collaborator: 20%)

33. Zarnke KB, McAlister FA, Campbell NR, Levine M, Schiffrin EL, **Tobe SW** , Grover S. The 2001 Canadian recommendations for the management of hypertension: Part one--Assessment for diagnosis, cardiovascular risk, causes and lifestyle modification. *Canadian Journal of Cardiology* 2002;**18**:604-24.
(Collaborator: 20%)

34. McAlister FA, Zarnke KB, Campbell NR, Feldman RD, Levine M, **Tobe SW**, Mahon J. The 2001 Canadian recommendations for the management of hypertension: Part two--Therapy. *Canadian Journal of Cardiology* 2002;**18**:625-41.
(Collaborator: 20%)

35. **Tobe S**, Epstein M. The use of calcium antagonists in the treatment of hypertensive persons with kidney disease. [Review] [21 refs]. *Current Hypertension Reports* 2002;**4**:191-4.
(Senior responsible author/principal author:90%)

36. **Tobe SW**, McFarlane PA, Naimark, DM. Microalbuminuria in Diabetes mellitus. CMAJ 9-3 2002 167:499-503
(Senior responsible author/principal author: 90%)

37. **Tobe, SW**. Update on calcium antagonists and the kidney. *Current Opinion in Nephrology and Hypertension* Vol 12 No 3 May 2003
(Senior responsible author/principal author: 90%)

38. **SW Tobe**, P. Aujla, AA Walele, MJ. Oliver, DMJ Naimark, N Perkins, M. Beardsall. A Novel Regional Citrate Anticoagulation Protocol for CRRT Using Only Commercially Available Solutions. Journal of Critical Care Vol 18, No 2 June, 2003 (Senior responsible author/principal author: 90%)

39. Abramov D, Tamariz M, Fremes S, **Tobe S**, Christakis G, Guru V and Goldman B. Impact of preoperative renal dysfunction on cardiac surgery results. Asian Cardiovas Thorac Ann 2003: 11:42-47
(Collaborator: 20%)

40. Baker B, Szalai JP, Paquette M and **Tobe S**. Marital Support, Spousal contact and the course of mild hypertension. J Psychosom Res 2003 55:229-233
(Senior responsible author: 90%)

41. Lok CE, Stanley KE, Hux JE, Richardson R, **Tobe SW** and Conly J. Hemodialysis infection prevention with polysporin ointment. J Am Soc Neph 2003 14:169-179
(Collaborator: 20%)

42. McFarlane P, Houlden R, Harris SB, **Tobe SW.** Nephropathy: Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Can J Diabetes: Dec 2003 27: Supp 2
(Senior responsible author: 40%)

43. **S Tobe**, A Ra. Acute Interstitial Nephritis due to Pantoprazole. Annals Of Pharmacology: 38: January 2004 (Senior responsible author/principal author: 90%)

44. Graansma C, Liu T, **Tobe S**. A simple solution to pseudoarrhythmia during continuous renal replacement therapy. CANNT J 2004 Oct ; 14(4):24-25 (Senior Responsible Author: 20%)

45. S Tailor, S Walker, **S Tobe,** T Yassa, L Awdishu. Pharmacokinetics of Oral Ciproflaxacin in Continuous Cycling Peritoneal Dialysis. Peritoneal Dialysis International. (Collaborator: 20%)

46. Yeung SM, Walker SE, Tailor SA, Awdishu L, Tobe S, Yassa T: Pharmacokinetics of oral ciprofloxacin in continuous cycling peritoneal dialysis. Perit Dial Int 24:447-453, 2004

47. Hemmelgarn BR, McAllister FA, Myers MG, McKay DW, Bolli P, Abbott C, Schiffrin EL, Grover S, Honos G, Lebel M, Mann K, Wilson T, Penner B, Tremblay G, Tobe SW, Feldman RD: The 2005 Canadian Hypertension Education Program recommendations for the management of hypertension: Part 1 - Blood pressure measurement, diagnosis and assessment of risk. Can J Cardiol 21:645-656, 2005

48. Khan NA, McAlister FA, Lewanczuk RZ, Touyz RM, Padwal R, Rabkin SW, Leiter LA, Lebel M, Herbert C, Schiffrin EL, Herman RJ, Hamet P, Fodor G, Carruthers G, Culleton B, Dechamplain J, Pylypchuk G, Logan AG, Gledhill N, Petrella R, Campbell NR, Arnold M, Moe G, Hill MD, Jones C, Larochelle P, Ogilvie RI, Tobe S, Houlden R, Burgess E, Feldman RD: The 2005 Canadian Hypertension Education Program recommendations for the management of hypertension: Part II - Therapy. Can J Cardiol 21:657-672, 2005

49. Article title: Impact of Job and Marital Strain on Ambulatory Blood Pressure: Results from the Double Exposure Study Reference: AJH11667Journal title: American Journal of Hypertension Corresponding author: Dr. Sheldon W. Tobe First author: Dr. Sheldon W Tobe Citation Information: Vol. 18/8 pp 1046-1051DOI information: 10.1016/j.amjhyper.2005.03.734

PUBLICATIONS AND PAPERS – IN PRESS

50. Tobe, S. W., Kiss, A., Szalai, J. P., Perkins, N. J., Tsigoulis, M., and Baker, B. Impact of Job and Marital Strain on Ambulatory Blood Pressure: Results from the Double Exposure Study. American Journal of Hypertension . In Press 2005.

51. Tobe, S. W., Kiss, A., Szalai, J. P., Perkins, N. J.,Sainsbury, S., Soberman, H., and Baker, B. Gender Alcohol and Hypertension: Results from the Double Exposure Study. American Journal of Hypertension . In Press 2005.

PUBLICATIONS AND PAPERS – Non-refereed

1. Manuel MA, **Tobe SW**, Mandel D, Saiphoo CS. A diagnostic approach to renal disease. *Modern Medicine of Canada.* 1986; 41(9).
(Co-principal author: 60%)

2. Blendis LM, Morali G, Legault L, **Tobe SW**, Floras JS, Skorecki KL. Natriuretic Factors. *Gastroenterology International.* Vol 5, No 4, pp 257-261,1992.
(Collaborator: 20%)

3. Mason P, **Tobe SW**. CCB's and the High Risk Patient-What are the Benefits? *The Medical Post.* October 5, 1999.
(Co-prinicpal author: 60%)

4. **Tobe SW**. Vasopeptidase Inhibition: Update on Renal Protection and Hypertension. *Physician Perspective.* May 2000.
(Most responsible author: 100%)

5. **Tobe SW**. Acute Renal Failure: Multiple Causes and Multiple Complications. *Geriatrics & Aging.* December 2000
(Most responsible author: 100%)

6. Pepperell C, **Tobe SW**. An Approach to Acute Renal Failure. *Canadian Journal of Diagnosis.* February 2001
(Co-principal author: 60%)

7. **Tobe SW**. COX-2 Inhibitors in Patients with Renal Failure. *Patient Care.* February 2001. (Most responsible author: 100%)

8. **Tobe SW**. Hypertension and Chronic Renal Failure: Novel Treatment Approaches. *Physicians Perspective.* March 2001. (Most responsible author: 100%)

9. Canadian Hypertension Recommendations Working Group. Summary of the 2000 Canadian Hypertension Recommendations. *Canadian Journal of Cardiology.* 2001;17: 535-38.
(Collaborator: 20%)

10. Canadian Hypertension Recommendations Working Group. Summary of the 2000 Canadian Hypertension Recommendations. *Perspectives in Cardiology.* 2001; 17:17-25.
(Collaborator: 20%)

11. Canadian Hypertension Recommendations Working Group. Summary of the 2000 Canadian Hypertension Recommendations. *Hypertension Canada.* 2001; bulletin 67:4,7.
(Collaborator: 20%)

12. Canadian Hypertension Recommendations Working Group. Summary of the 2000 Canadian Hypertension Recommendations. *Canadian Pharmacy Journal.* March 2001: 30-3.
(Collaborator: 20%)

PUBLICATIONS AND PAPERS – Non-refereed (Con't)

13. Canadian Hypertension Recommendations Working Group. Summary of the 2000 Canadian Hypertension Recommendations. *Canadian Family Physician.* 2001;47:793-4. (Collaborator: 20%)

14. Canadian Hypertension Recommendations Working Group. Summary of the 2000 Canadian Hypertension Recommendations. *Journal of Cardiovascular Nursing, The Canadian Internist.* Spring 2991; 11-13.
(Collaborator: 20%)

15. Canadian Hypertension Recommendations Working Group. Summary of the 2000 Canadian Hypertension Recommendations. *Les Actualites du Coeur.* 2001; 6 (insert).
(Collaborator: 20%)

16. **Tobe SW**. Renal Vascular Hypertension: Contemporary Approaches. *Hypertension Canada.* September 2001. (Most responsible author: 100%)

17. Epstein M, **Tobe SW**. What is the Optimal Strategy to Intensify Blood Pressure Control and Prevent Progression of Renal Failure? *Current Hypertension reports.* October 2001.
(Co-principal author: 60%)

18. **Tobe SW**, Drouin D. Hypertension: A Marker for Risk. Clinical Focus: *Hypertension and Microalbuminuria,* 2001 (Senior responsible author: 90%)

19. Cherukuri S, **Tobe SW.** Isolated Systolic Hypertension in the Elderly. *Geriatrics and Aging*: 6:2 February 2003 (Co-principal author: 60%)

20. **S Tobe**. Ease in control of diastolic vs systolic pressure. Corridor Consultations: Patient Care. 14:11 2003
(Most responsible author: 100%)

21. **Tobe, SW et al**. "Quenching the Fire: An update on calcium channel blockers and atheroprotection". *Medical Post:* vol 39 No 46 Dec 16, 2003.
(Senior Responsible author: 60%)

22. McFarlane P, **Tobe S,** Houlden R, Harris SB. Canadian Diabetes Association Clinical Practice Guidelines: Nephropathy. Dec 2003 (Collaborator: 20%)

23. 2005 Canadian Hypertension Education Program Recommendations; What Are The New Messages? Perspectives in Cardiology July 2005. (Collaborator: 20%)

BOOKS

Tobe, SW and Leiter, L. Risk Management in Cardiovascular Disease: Hypertension and other risk factors in Diabetes. July, 2002. Denis Drouin and Peter Liu, ed. Volume 1. Elsevier Science Ltd, Exerpta Medica Publications, Montreal Canada.
(Co-principal author)

BOOK CHAPTERS

1. Richardson RMA, **Tobe SW**. Approach to the Patient with Polyuria or Nocturia. Chapter 132. Textbook of Internal Medicine. Second Ed. Kelley, 1992, J.B. Lippincott Company. (Co-principal author)

2. Miller J, **Tobe SW**, Skorecki KL. Control of ECF Volume and Pathophysiology of Edema Formation. Chapter 20:817-872. The Kidney. Fifth Ed. Brenner, BM, W.B. Saunders Co., 1995.
(Collaborator)

3. Richardson RMA, **Tobe SW**. Approach to the Patient with Polyuria or Nocturia. Chapter 132. Textbook of Internal Medicine. Third Ed. Kelley, J.B. Lippincott Co., 1996.
(Co-principal author)

4. **Tobe, SW**. Approaches to maximize cardiovascular risk reduction in people with kidney disease. The Kidney and Hypertension: George L. Bakris, Ed. 2004: Martin Dunitz Group.
(Most responsible author)

PRESENTATIONS AND SPECIAL LECTURES

INVITED LECTURESHIP: LOCAL

1991	Understanding Erythropoietin The Kidney Foundation of Canada, Ontario Branch Annual Meeting Toronto, Canada.
March 1995	Erythropoietin in Dialysis Current Topics in Transfusion Medicine Conference, Red Cross Society Mitchener Institute, Toronto
March 1997	Clinical Research in the Community South Western Ontario Nephrology Group Toronto, Ontario
May 1997	Hypomagnesemia in a Patient with Gittelman's Syndrome Wellesley Hospital Grand Rounds Toronto, Ontario
Nov 1997	Provincial Overview of ESRD Ontario Forum on End Stage Renal Disease Kidney Foundation of Canada Toronto, Ontario
Oct 1999	Antagonism of AT1 Receptors: New Strategies for the Management of Cardiovascular Disease Toronto, Ontario
April 2002	University Health Network, Toronto, Ontario. Hypertension in Dialysis. City Wide Rounds, April 24, 2002
October 2002	University of Toronto Department of Medicine Grand Rounds. Medical Aspects of Renal Protection
October 2003	Canadian Cardiovascular Congress Cardiovascular Adverse effects of Cox-2 Inhibitors and other non-steroidal anti-inflammatory drugs Diabetes and Hypertension: The Emerging Epidemic Poster and Oral Session Moderator Toronto, Ontario
October 2004	Prevention in Renal Disease International Conference Toronto, Ontario Blood Pressure and the decline of kidney function in the elderly
November 2004	Kidney Foundation of Ontario Patient and Family Symposium Research Update: Paving the way for a Better Tomorrow Toronto, Ontario
May 2005	Clinical Science: CKD in Aboriginal Populations Chairs: Dr. Sheldon Tobe and Dr. Marcello Tonelli

INVITED LECTURSHIP: PROVINCIAL

June 1997	Diabetic Nephropathy, Microalbuminuria & Screening Kingston Nephrology Grand Rounds Kingston, Ontario
June 1998	Canadian Consensus Conference for the Revision of Clinical Practice Guidelines for the Treatment of Hypertension in Canada. Leader: Section on Hypertension in Chronic Renal Insufficiency. London, Ontario
Sept 1999	Ace Inhibition in Diabetic Nephropathy. Diabetes Faculty Workshop: A Focus on Hypertension and Microvascular Complications in Diabetes Caledon, Ontario
Dec 1999	Renal Effects of COX-2 Inhibitors Second Candian Consensus Conference: An Evidence-Based Approach to Prescribing NSAIDS Cambridge, Ontario
May 2001	Ontario Hypertension Society Angiotensin II Antagonists and the Cardiovascular Continuum Haliburton, Ontario

INVITED LECTURSHIP: NATIONAL

April 1999	Nephrology Grand Rounds, Universite de Laval Microalbuminuria and Coronary Artery Disease-Is There a Link? Quebec City, Quebec
	Nephrology Visiting Professor, Universite de Laval Continuous Renal Replacement Therapy-What's New? Quebec City, Quebec
Sept 1999	Cardiovascular Risk, Diabetes & The Kidney Edmonton, Alberta
	Angiotensin II Receptor Blockers: A Critical Review Canmore, Alberta
Feb 2000	COX-2 Specific Inhibition and Renal Implications COX-2 Specific Inhibition: Beyond the GI Tract Lake Louise, Alberta
Mar 2000	Chair, Clinical Pathology Conference Canadian Society of Nephrology Montreal, Quebec

INVITED LECTURSHIP: NATIONAL (Continued)

June 2000	Vancouver General Hospital, Nephrology Rounds Importance of Treating Hypertension and Preventing Target Organ Damage Vancouver, B.C.
June 2000	Hypertension in Diabetic Patients Montreal, Quebec
Sept 2000	Foothills Hospital Intensive Care Grand Rounds Bicarbonate Dialysis Solutions for CRRT Calgary, Alberta
March 2001	Canadian Society of Nephrology Hypertension in Chronic Renal Failure Blood Pressure Control in HD patients: the dippers, non dippers and beyond. Vancouver, B.C.
October 2002	Canadian Cardiovascular Congress Renal and Renovascular Hypertension. Hypertension and Diabetes. Edmonton, Alberta
January 2003	St. Paul's Hospital Nephrology Grand Rounds Citrate Regional Anticoagulation for CRRT Vancouver, B.C.
January 2004	National Aboriginal Diabetes Association Conference DREAM 3: Lifestyle Intervention Sub-study Vancouver, British Columbia
February 2004	First Nations Home and Community Care Challenge Conference DREAM Research Projects Vancouver, British Columbia
May 2005	Canadian Society of Nephrology: Chair Concurrent Symposia CKD in Aboriginal Populations Calgary, Alberta

INVITED LECTURSHIP: INTERNATIONAL

Jan 1992	Modification of Multidrug Resistance Guest Lecturer, Shaare Tzedek Medical Centre Jerusalem, Israel
Nov 1994	Diabetic Nephropathy Guest Lecturer, Shaare Tzedek Medical Centre Jerusalem, Israel
Nov 1994	Diabetic Nephropathy Guest Lecturer, Rambam Health Sciences Centre, Technion University Haifa, Israel

INVITED LECTURSHIP: INTERNATIONAL (Continued)

July 1995	Continuous Renal Replacement Therapy Guest Lecturer, Rambam Health Sciences Centre, Technion University Haifa, Israel
Feb 1996	Bicarbonate Dialysate for Renal Replacement Therapy Guest Lecturer, City Wide Nephrology Rounds, University of South Florida Tampa, Florida
Sept 1999	Diabetic Nephropathy: Approach to the Patient with Microalbuminuria. Future of Dialysis. Critical Care Nephrology Continuous Renal Replacement Therapy. Sixth Budapest Nephrology School (International Society of Nephrology) Budapest, Hungary
Jan 2000	State-of-the-Art Hypertension Specialists Role in Moving Knowledge to Practice Palm Springs, California
Aug 2000	Annual Pfizer Asian Scientific Symposium Renal Protection in the Hypertensive Diabetic: What is the Evidence? Hong Kong
March 2001	Sixth International Conference on Continuous Renal Replacement Therapy Replacement and Dialysate Solutions for CRRT. San Diego, California
Oct 2001	World Congress of Nephrology Reducing the Hypertensive Mortality in Dialysis Patients: Is Systolic Pressure the Only Measurement of Concern? San Francisco, California
Nov 2001	Nephrology Clinical Conference, Vanderbilt University School of Medicine. Citrate Regional Anticoagulation for CRRT
Jan 2002	Israel - Israel Institute of Technology/Bruce Rappaport Faculty of Medicine Recent Hypertension Guidelines in Patients with Renal Failure/ Citrate Regional Anticoagulation for CRRT
March 2002	Conference on Continuous Renal Replacement Therapies Citrate Anticoagulation for CRRT: Which Method? San Diego, California
	Conference on Continuous Renal Replacement Therapies Replacement and Dialysate Solutions for CRRT San Diego, California

INVITED LECTURSHIP: INTERNATIONAL (Continued)

April 2002	Clinical Nephrology Meetings 2002. National Kidney Foundation. Systolic Diastolic or Pulse Pressure – which is more important for Cardiovascular outcomes in Pre-dialysis Patients? Chicago, Illinois.
September 2002	University of California and Los Angeles Regional Renal Grand Rounds (Kaiser Permanente – Southern California Permanente Medical Group) CRRT: An Update
October 2002	American Association of Nephrology – Renal Week 2002 Postgraduate Lecturer and Presenter The Increasing Crisis of Cardiovascular Disease in Patients with Renal Failure. Reducing the Hypertensive Mortality in Dialysis Patients: Systolic or Pulse Pressure: What's more important: Philadelphia, Pennsylvania
March 2003	8th International Conference on Continuous Renal Replacement Therapies. Solutions for CRRT San Diego, California
November 2003	American Society of Nephrology Post Graduate Education Speaker: Reducing the Hypertensive Mortality in Dialysis Patients: Systolic or Diastolic Pulse Pressure – What's more Important? Official Evening Symposium: Coronary Artery Disease in the Diabetic with CKD: Drugs, Surgery and Contrast Dye San Diego, California
January 2004	23rd Annual Advanced Nephrology: Nephrology for the Consultant Achieving Acid Base Balance in CRRT: Do we have a solution? San Diego, California
March 2004	9th International Conference on Continuous Renal Replacement Therapy. Solutions for CRRT San Diego, California
May 2004	7th Asian Cardiology Symposium Targeting CVD Risks: Tackling Diabetes Nephropathy Seoul, Korea
March 2005	Pfizer Taipei ESROC
March 2005	10th International Conference on Continuous Renal Replacement Therapy. Solutions for CRRT San Diego, California
June 2005	Singapore World Congress of Nephrology Renal Protection in diabetes New evidence & New concepts of lipid lowering in diabetes Singapore

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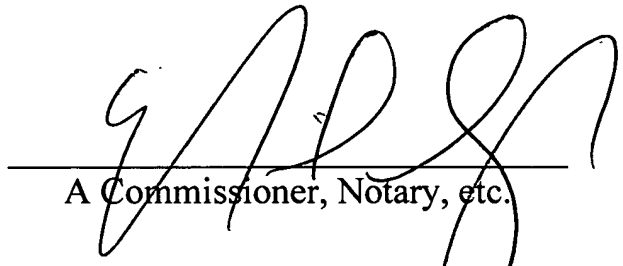
PATENTS

1999 **Sheldon W. Tobe**
U.S. and Canadian Patent Granted – Sterile Bicarbonate Concentrate for CRRT

This is EXHIBIT B referred to in the
Declaration of Sheldon William Tobe, M.D.
sworn this 8th day of February, 2006



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NEIL HARVEY HUGHES, Notary Public, Province of Ontario,
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Patent and Trademark Agents.
Expires March 30, 2007.

This is EXHIBIT C referred to in the
Declaration of Sheldon William Tobe, M.D.
sworn this 8th day of February, 2006

A Commissioner, Notary, etc.

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(54) Title: BIOCHEMICALLY BALANCED PERITONEAL DIALYSIS SOLUTIONS

(57) Abstract

A peritoneal dialysis solution that is biochemically balanced to correct metabolic acidosis associated with chronic renal failure in a more physiological manner. The peritoneal dialysis solution has a physiological pH, e.g., pH of 7.0 to 7.4, and contains bicarbonate at a concentration that is found in normal blood. Additionally, the solution contains carbon dioxide at a partial pressure that is similar to partial pressure of carbon dioxide found in normal blood. The peritoneal dialysis solution also contains a weak acid with a pKa of less than 5.0.

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GA	Gabon				

SPECIFICATION

TITLE

"BIOCHEMICALLY BALANCED PERITONEAL DIALYSIS SOLUTIONS"

BACKGROUND OF THE INVENTION

The present invention relates generally to peritoneal dialysis. More specifically, the present invention relates to peritoneal dialysis solutions.

It is known to use dialysis to support a patient whose renal function has decreased to the point where the kidneys no longer sufficiently function. Two principal dialysis methods are utilized: hemodialysis; and peritoneal dialysis.

In hemodialysis, the patient's blood is passed through an artificial kidney dialysis machine. A membrane in the machine acts as an artificial kidney for cleansing the blood. Because it is an extracorporeal treatment that requires special machinery, there are certain inherent disadvantages with hemodialysis.

To overcome the disadvantages associated with hemodialysis, peritoneal dialysis was developed. Peritoneal dialysis utilizes the patient's own peritoneum as a semi-permeable membrane. The peritoneum is the membranous lining of the abdominal cavity that due to a large number of blood vessels and capillaries is capable of acting as a natural semi-permeable membrane.

In peritoneal dialysis, a dialysis solution is introduced into the peritoneal cavity utilizing a catheter. After a sufficient period of time, an exchange of solutes between the dialysate and the blood is achieved. Fluid removal is achieved by providing a suitable osmotic gradient from the blood to the dialysate to permit water outflow from the blood. This allows the

proper acid-base of electrolytes and fluid balance to be returned to the blood and the dialysis solution is simply drained from the body cavity through the catheter.

A number of dialysis solutions have been utilized and suggested. One of the difficulties with dialysis solutions that are used for peritoneal dialysis is that they are not ideal solutions for maintaining acid base homeostasis. Metabolic acidosis is a catabolic event that can occur in peritoneal dialysis patients.

In this regard, the kidneys play a major role in the maintenance of the acid-base balance. In chronic renal failure, the acid generated from the metabolism of dietary proteins can lead to metabolic acidosis. Metabolic acidosis can have a profound and acute effect on the respiratory, cardiac, and/or nervous systems. Long term consequences of metabolic acidosis include protein malnutrition and skeletal diseases.

Lactate has been utilized in peritoneal dialysis solutions for the purpose of maintaining acid-base balance in peritoneal dialysis patients. Typical commercially available peritoneal dialysis solutions contain 35 to 40 mEq/L of lactate.

These solutions are adequate in maintaining acid-base balance in a number of dialysis patients. However, patients who are deficient in lactate metabolism and/or who also experience or suffer from hepatic failure or shock can develop lactic acidosis. This syndrome includes as characteristic symptoms hyperventilation, abdominal pain, and disturbances in consciousness while the patient receives lactate-containing peritoneal dialysis fluids.

An additional issue with respect to lactate peritoneal dialysis solutions is that a number of *in*

vitro studies performed with peritoneal cells indicate that altered cell function can occur when peritoneal cells are exposed to large concentrations of lactate. These changes in cell function can compromise host defense leading to increased rates of infection and damage to the peritoneal membrane.

In order to address this issue, peritoneal dialysis solutions in which lactate is completely replaced by bicarbonate have been proposed. However, in order to balance total body hydrogen ion content against metabolically generated hydrogen, and to maintain normal plasma carbonic acid and bicarbonate concentrations, it is necessary to use bicarbonate concentrations that are considerably in excess of normal. In this regard, bicarbonate concentration upwards of 38 mM/L are believed to be necessary.

Because it is necessary to maintain the solution at a physiological pH, the requirement of such a high bicarbonate solution requires a partial pressure of carbon dioxide (pCO_2) that is at least twice the physiologic pCO_2 (e.g., greater than 80 mmHg). Although such a solution may meet the metabolic needs of the patient, such a solution does not provide a physiological environment for the peritoneal cells in contact with the solution. Due to the differences in transport rates between bicarbonate and carbon dioxide, with such a solution, the intracellular hydrogen ion concentration of the cell's lining the peritoneal cavity, as well as those present in the peritoneal cavity, would be severely low placing them at a metabolic disadvantage. This metabolic disadvantage will increase more than would be expected if they share the extracellular environment of normal pH, but a supernormal bicarbonate and pCO_2.

There is therefore a need for a peritoneal dialysis solution that adequately addresses the problem of metabolic acidosis associated with end stage renal disease.

SUMMARY OF THE INVENTION

The present invention provides a peritoneal dialysis solution that is biochemically balanced to correct metabolic acidosis associated with chronic renal failure in a more physiological manner. The peritoneal dialysis solution has a physiological pH, e.g., pH of 7.0 to 7.4, and contains bicarbonate at a concentration that is found in blood involved in diffusive transport of solutes with dialysis fluid. This will block the loss of bicarbonate during peritoneal dialysis which is the case with present solutions. Additionally, the solution contains carbon dioxide at a partial pressure that is similar to partial pressure of carbon dioxide found in the blood capillaries. The peritoneal dialysis solution also contains a weak acid with a pKa of less than 5.0 at an amount needed to neutralize acid generated from endogenous metabolism. These weak acids are also the normal biochemical intermediates of glucose metabolism resulting in neutral end products.

To this end, the present invention provides a peritoneal dialysis solution including bicarbonate at a level of less than or equal to 30 mM/L, having a pCO_2 that is less than 60 mmHg, and including at least one weak acid selected from the group consisting of: lactate; pyruvate; citrate; isocitrate; cis-aconitase; α-ketoglutarate; succinate; fumarate; malate; and oxaloacetate.

In an embodiment of the peritoneal dialysis solution, bicarbonate is present in the solution at 25 mM/L.

In an embodiment of the peritoneal dialysis solution, the weak acid is present in an amount comprising approximately 10 mEq/L to about 20 mEq/L.

In an embodiment of the peritoneal dialysis solution, the pCO_2 of the solution is approximately the same as the pCO_2 of blood.

In an embodiment of the peritoneal dialysis solution, the solution has a pH of approximately 7.4.

In an embodiment of the peritoneal dialysis solution, the weak acids have a pKa of < 5.0.

In another embodiment, the present invention provides a peritoneal dialysis solution comprising:

Dextrose (hydrous) (g/dl)	1.5-4.25
Sodium (mEq/L)	100-140
Chloride (mEq/L)	70-110
Calcium (mEq/L)	0.0-4.0
Magnesium (mEq/L)	0.0-4.0
Bicarbonate (mEq/L)	20.0-30.0
Weak acid (mEq/L)	10.0-20.0

wherein the weak acid is chosen from the group consisting of: lactate; pyruvate; citrate; isocitrate; cis-aconitase; α-ketoglutarate; succinate; fumarate; malate; and oxaloacetate.

In an embodiment, the solution includes an osmotic agent other than dextrose.

In an embodiment, the present invention provides a method for correcting metabolic acidosis in a dialysis patient suffering or likely to suffer from same comprising the step of administering to a dialysis patient a peritoneal dialysis solution that has a

bicarbonate level and carbon dioxide partial pressure that is substantially similar to that found in the normal person's blood.

An advantage of the present invention is that it provides an improved peritoneal dialysis solution.

Another advantage of the present invention is that it provides bicarbonate to the patient when blood bicarbonate is below normal.

Still an advantage of the present invention is that it removes bicarbonate when blood bicarbonate is above normal.

Another advantage of the present invention is that it provides a biochemically balanced peritoneal dialysis solution.

Furthermore, an advantage of the present invention is that it provides a peritoneal dialysis solution that corrects metabolic acidosis associated with end stage renal disease.

Moreover, an advantage of the present invention is that it provides a peritoneal dialysis solution that balances bicarbonate at a normal concentration with a pCO_2 at normal partial pressure.

Further, an advantage of the present invention is that the dialysis solution provides an additional contribution of bicarbonate by diffusion of bicarbonate to offset the end balance of the metabolic hydrogen load and *vice versa* for a supernormal concentration.

Another advantage of the present invention is that it provides a peritoneal dialysis solution at a physiological pH.

Additional features and advantages of the present invention are described in, and will be apparent from,

the detailed description of the presently preferred embodiments.

DETAILED DESCRIPTION

OF THE PRESENTLY PREFERRED EMBODIMENTS

The present invention provides improved peritoneal dialysis solutions. The solutions are biochemically balanced to correct metabolic acidosis that is associated with chronic renal failure. Pursuant to the present invention, the solutions are biochemically balanced in a more physiological manner than prior peritoneal solutions.

To this end, the present invention provides peritoneal dialysis solutions that contain bicarbonate at a more physiological level, e.g., at a level substantially equivalent to that found in normal blood.

The peritoneal dialysis solution of the present invention, in an embodiment, includes bicarbonate present at a level of approximately 20 mM/L to about 30 mM/L. In a most preferred embodiment, bicarbonate is present at a level of 25 mM/L.

Additionally, the solution contains carbon dioxide at a partial pressure that is less than 60 mmHg. In a preferred embodiment the pCO_2 of the solution is similar to the partial pressure of carbon dioxide found in blood capillaries.

Further, preferably, the dialysis solutions have a pH of 7.4. Therefore, the solution, although balanced biochemically, is a physiologically acceptable solution.

Additionally, the solutions include a weak acid with a pKa of less than 5. These weak acids are chosen so as to be normal biochemical intermediates of glucose metabolism. Preferably, the weak acids are chosen from

the group consisting of: lactate; pyruvate; citrate; isocitrate; cis-aconitase; α-ketoglutarate; succinate; fumarate; malate; and oxaloacetate. These acids can be present either alone or in combination in the solution. Preferably, the weak acids are present at a level of approximately 10 to about 20 mEq/L. Preferably, the weak acid are present mainly as sodium salts. The weak acid is present in an amount that would offset the daily metabolic hydrogen production of approximately 1 mEq/kg/day.

Pursuant to the present invention, any osmotic agent can be used in the solution. For example, dextrose, maltodextrin, glycerol, polyglucose, polypeptides and amino acids can be used as the osmotic agent.

Preferably, the peritoneal dialysis solution, if it contains dextrose as an osmotic agent, has a general composition such as that set forth below:

Dextrose (hydrous) (g/dl)	1.5-4.25
Sodium (mEq/L)	100-140
Chloride (mEq/L)	70-110
Calcium (mEq/L)	0.0-4.0
Magnesium (mEq/L)	0.0-4.0
Bicarbonate (mEq/L)	20.0-30.0
Weak acid (mEq/L)	10.0-20.0
pH	7.0-7.4

Preferably, solutions containing an osmotic agent other than dextrose composition have the general composition:

Osmotic agent (mM/L)	1-200
Sodium (mEq/L)	100-140
Chloride (mEq/L)	70-110
Calcium (mEq/L)	0.0-4.0
Magnesium (mEq/L)	0.0-4.0

Bicarbonate (mEq/L)	20.0-30.0
Weak Acid (mEq/L)	10-20.00
pH	7.0-7.4

The peritoneal dialysis solutions of the present invention balance bicarbonate at normal concentrations and have a pCO_2 at normal partial pressure. The weak acid under usual circumstances will have an infinite gradient from dialysate to blood. Thus, the weak acid can be expected to perform in a relatively predictable manner in correcting the metabolic acidosis of chronic uremia.

Due to the composition of the present invention, should the patient's bicarbonate level drop below prescribed normal blood figure of 25 mM/L, then there will be an additional contribution by diffusion of bicarbonate to offset the unbalanced metabolic hydrogen load and *vice versa* for a supernormal concentration. Phrased in a different manner, the solution has a built in servo mechanism around the figure of 25 mM/L for bicarbonate. A pure bicarbonate solution at higher than normal concentrations does not offer this benefit.

By way of example, and not limitation, examples of specific peritoneal dialysis solutions of the present invention will now be given.

EXAMPLE NO. 1

Dextrose (hydrous)(g/dl)	1.5
Sodium (mEq/L)	132
Chloride (mEq/L)	96
Calcium (mEq/L)	3.5
Magnesium (mEq/L)	0.5
Bicarbonate (mEq/L)	25.00
Lactate (mEq/L)	15
pH	7.4

EXAMPLE NO. 2	
Dextrose (hydrous)(g/dl)	2.5
Sodium (mEq/L)	132
Chloride (mEq/L)	96
Calcium (mEq/L)	3.5
Magnesium (mEq/L)	0.5
Bicarbonate (mEq/L)	25.00
Lactate (mEq/L)	15.0
pH	7.4
EXAMPLE NO. 3	
Dextrose (hydrous)(g/dl)	4.25
Sodium (mEq/L)	132
Chloride (mEq/L)	96
Calcium (mEq/L)	3.5
Magnesium (mEq/L)	0.5
Bicarbonate (mEq/L)	25.00
Lactate (mEq/L)	15.0
pH	7.4
EXAMPLE NO. 4	
Dextrose (hydrous)(g/dl)	1.5
Sodium (mEq/L)	132
Chloride (mEq/L)	96
Calcium (mEq/L)	3.5
Magnesium (mEq/L)	0.5
Bicarbonate (mEq/L)	20
Lactate (mEq/L)	20
pH	7.4
EXAMPLE NO. 5	
Dextrose (hydrous)(g/dl)	2.25
Sodium (mEq/L)	132
Chloride (mEq/L)	96
Calcium (mEq/L)	3.5
Magnesium (mEq/L)	0.5

Bicarbonate (mEq/L)	20.0
Lactate (mEq/L)	20.0
pH	7.4

EXAMPLE NO. 6

Dextrose (hydrous)(g/dl)	4.25
Sodium (mEq/L)	132
Chloride (mEq/L)	96
Calcium (mEq/L)	3.5
Magnesium (mEq/L)	0.5
Bicarbonate (mEq/L)	20
Lactate (mEq/L)	20
pH	7.4

EXAMPLE NO. 7

Dextrose (hydrous)(g/dl)	1.5
Sodium (mEq/L)	132
Chloride (mEq/L)	96
Calcium (mEq/L)	3.5
Magnesium (mEq/L)	0.5
Bicarbonate (mEq/L)	30.0
Lactate (mEq/L)	10.0
pH	7.4

EXAMPLE NO. 8

Dextrose (hydrous)(g/dl)	2.50
Sodium (mEq/L)	132
Chloride (mEq/L)	96
Calcium (mEq/L)	3.5
Magnesium (mEq/L)	0.5
Bicarbonate (mEq/L)	30.0
Lactate (mEq/L)	10.0
pH	7.4

EXAMPLE NO. 9

Dextrose (hydrous)(g/dl)	4.25
Sodium (mEq/L)	132

Chloride (mEq/L)	96
Calcium (mEq/L)	3.5
Magnesium (mEq/L)	0.5
Bicarbonate (mEq/L)	30.0
Lactate (mEq/L)	10.0
pH	7.4

It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present invention and without diminishing its attendant advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

WE CLAIM:

1. A peritoneal dialysis solution including bicarbonate at a level of greater than or equal to 20 mM/L and less than or equal to 30 mM/L, having a carbon dioxide partial pressure that is less than 60 mmHg and including at least one weak acid present in an amount comprising approximately 10 mEq/L to about 20 mEq/L selected from the group consisting of: lactate; pyruvate; citrate; isocitrate; cis-aconitase; α-ketoglutarate; succinate; fumarate; malate; and oxaloacetate.

2. The peritoneal dialysis solution of Claim 1 wherein bicarbonate is present in the solution at 25 mM/L.

3. The peritoneal dialysis solution of Claim 1 wherein the carbon dioxide partial pressure of the solution is approximately the same as the carbon dioxide partial pressure of blood.

4. The peritoneal dialysis solution of Claim 1 wherein the solution has a pH of approximately 7.0 to about 7.4.

5. The peritoneal dialysis solution of Claim 1 wherein the weak acids have a pKa of < 5.0.

6. The peritoneal dialysis solution of Claim 1 wherein the carbon dioxide partial pressure of the solution is approximately the same as the carbon dioxide partial pressure of blood.

7. A peritoneal dialysis solution comprising:

Dextrose (hydrous) (g/dl)	1.5-4.25
Sodium (mEq/L)	100-140
Chloride (mEq/L)	70-110
Calcium (mEq/L)	0.0-4.0
Magnesium (mEq/L)	0.0-4.0

Bicarbonate (mEq/L)	20.0-30.0
Weak acid (mEq/L)	10.0-20.0

wherein the weak acid is at least one acid chosen from the group consisting of: lactate; pyruvate; citrate; isocitrate; cis-aconitase; α-ketoglutarate; succinate; fumarate; malate; and oxaloacetate.

8. The peritoneal dialysis solution of Claim 7 wherein the solution has a pH of approximately 7.0 to about 7.4.

9. The peritoneal dialysis solution of Claim 7 wherein the weak acids have a pKa of < 5.0.

10. The peritoneal dialysis solution of Claim 7 wherein the carbon dioxide partial pressure is less than 60 mmHg.

11. The peritoneal dialysis solution of Claim 7 wherein the carbon dioxide partial pressure of the solution is approximately the same as the carbon dioxide partial pressure of normal blood.

12. A peritoneal dialysis solution comprising:

Dextrose (hydrous) (g/dl)	1.5-4.25
Sodium (mEq/L)	100-140
Chloride (mEq/L)	70-110
Calcium (mEq/L)	0.0-4.0
Magnesium (mEq/L)	0.0-4.0
Bicarbonate (mEq/L)	20.0-30.0
Weak acid (mEq/L)	10.0-20.0

wherein the weak acid is at least one acid chosen from the group consisting of: lactate; pyruvate; citrate; isocitrate; cis-aconitase; α-ketoglutarate; succinate; fumarate; malate; and oxaloacetate; and

the solution has a carbon dioxide partial pressure that is substantially similar to the carbon dioxide

partial pressure of a normal subject's blood and the solution has a pH of 7.0 to 7.4.

13. A method for correcting metabolic acidosis in a dialysis patient suffering or likely to suffer from same comprising the step of:

administering to a patient a peritoneal dialysis solution that has a bicarbonate level and carbon dioxide partial pressure that are substantially similar to that found in the patient's blood.

14. The method of Claim 13 wherein the solution comprises:

Dextrose (hydrous) (g/dl)	1.5-4.25
Sodium (mEq/L)	100-140
Chloride (mEq/L)	70-110
Calcium (mEq/L)	0.0-4.0
Magnesium (mEq/L)	0.0-4.0
Bicarbonate (mEq/L)	20.0-30.0
Weak acid (mEq/L)	10.0-20.0

15. The method of Claim 13 including the step of administering to the patient a weak acid that is present in the solution in an amount that offsets the daily hydrogen production of approximately 1 mEq/kg/day.

16. The method of Claim 15 wherein the weak acids have a pKa of < 5.0.

17. The method of Claim 14 wherein the solution has a pH of approximately 7.0 to about 7.4.

18. The method of Claim 13 wherein the solution does not include lactate.

19. The method of Claim 15 wherein the weak acid is present in the solution at a level of approximately 10 to about 20 mEq/L.

INTERNATIONAL SEARCH REPORT

Intern. ..al Application No
PCT/US 95/06784

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K33/14 A61M1/16 A61M1/28 //(A61K33/14,33:10,33:00, 31:70,31:19)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 399 549 (FRESENIUS AG) 28 November 1990 see the whole document -----	1-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
10 October 1995	27. 10. 95
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Leherte, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/US95/06784

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13-19
because they relate to subject matter not required to be searched by this Authority, namely:
"Remark: Although claims 13-19 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition."

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

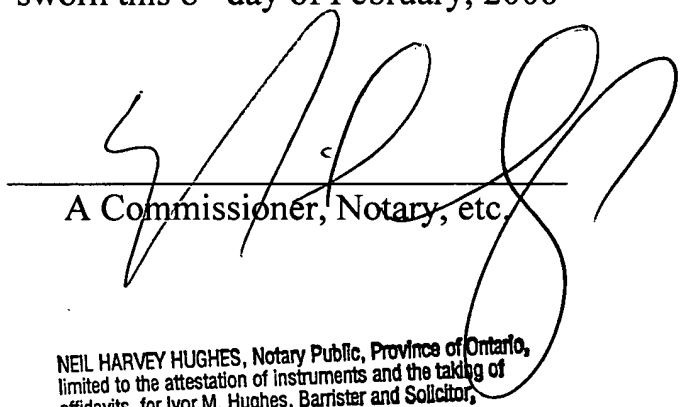
INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/US 95/06784

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0399549	28-11-90	DE-A-	3917251	29-11-90
		AU-B-	633917	11-02-93
		AU-B-	5581390	29-11-90
		CA-A-	2017531	26-11-90
		DE-D-	59003505	23-12-93
		ES-T-	2047757	01-03-94
		JP-A-	3103265	30-04-91
		US-A-	5211643	18-05-93

This is EXHIBIT D referred to in the
Declaration of Sheldon William Tobe, M.D.
sworn this 8th day of February, 2006



A Commissioner, Notary, etc.

NEIL HARVEY HUGHES, Notary Public, Province of Ontario,
limited to the attestation of instruments and the taking of
affidavits, for Ivor M. Hughes, Barrister and Solicitor,
Patent and Trademark Agents.
Expires March 30, 2007.

Original Paper

NEPHRON

Nephron 1996;72:424–428

Calcium-Free Hemodialysis for the Management of Hypercalcemia

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Key Words
Calcium-free hemodialysis
Hypercalcemia
Urea kinetics

Abstract
The drug therapies for hypercalcemia of malignancy have been known to be associated with either limited efficacy or cumulative toxicity in patients with advanced renal failure. To establish the guidelines for the use of dialysis and to determine its optimal prescription for hypercalcemia, calcium-free hemodialysis was performed in 6 hypercalcemic patients with renal failure not responding enough to forced saline diuresis. Calcium-free dialysate contained sodium 135, potassium 2.5, chloride 108, magnesium 0.75, bicarbonate 30 mmol/l. Mean hemodialysis time was 160 ± 27 min and mean Kt/V urea was 0.75 ± 0.2. Plasma calcium concentrations fell from a mean value of 2.92 ± 0.21 mmol/l (range 2.55–3.25) to 2.58 ± 0.16 mmol/l at 1 h of hemodialysis and to 2.16 ± 0.33 mmol/l (range 1.63–2.53) following 2–3 h of hemodialysis. The ionized calcium (n = 4) decreased from 1.44 ± 0.14 mmol/l to 0.99 ± 0.2 mmol/l. No patient showed any hypocalcemic symptoms and signs during hemodialysis. The rate of decrease in plasma calcium did not appear to produce adverse effects in any of the patients. There was a significant positive correlation between the decrease in plasma calcium concentration and the Kt/V urea ($y = 1.4x - 0.29$, $r = 0.92$, $p < 0.01$). We conclude that calcium-free hemodialysis is indicated when the presence of severe renal failure prevents the administration of large volumes of intravenous fluids to hypercalcemic patients. The amount of dialysis (Kt/V urea) can be used to predict the decrease in plasma calcium concentration during calcium-free hemodialysis.

Introduction

The usual therapeutic measures in hypercalcemic crisis are based on an increase of renal calcium excretion and the reduction of calcium mobilization from the bone [1]. Unless specifically contraindicated, initial treatment should consist of hydration and maintenance of a saline diuresis since extracellular volume depletion is always invariably present and contributes to the hypercalcemia [2]. However, forced saline diuresis may not be safe or effective enough particularly in patients with advanced renal failure. Other therapeutic approaches to hypercalcemia are either ineffective, slow in action, or may have serious disadvantages, especially in patients with advanced renal failure [1]. Although short-term hemodialysis is generally mentioned as a potential therapy in several

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articles [3–5], actual prescription of such an approach has not been properly defined yet.

To establish the guidelines for the use of dialysis and to determine its optimal prescription for hypercalcemia, calcium-free hemodialysis was performed in 6 patients with malignancy-associated hypercalcemia and renal failure not responding enough to forced saline diuresis.

Materials and Methods

A prospective study on calcium-free hemodialysis was performed in 6 hypercalcemic patients (mean age 57 years, range 42–65). The causes of their hypercalcemia were multiple myeloma (n = 3), lung cancer (n = 2), and renal cell carcinoma (n = 1) (table 1). Two patients were female and 4 were male. All had been in hypercalcemia and renal failure at the beginning of hemodialysis and had received prior treatment with forced saline diuresis without success. None of the patients had received other forms of therapy in order to control the plasma calcium concentration except forced saline diuresis with furosemide. Twelve sessions of calcium-free hemodialysis were performed in 6 patients without side effects during the study period. Urea kinetic data of 8 of 12 hemodialysis sessions are presented here.

Vascular access was achieved with single-lumen femoral vein catheters. Cuprophan hollow-fiber dialyzers with a surface area of 0.8 m^2 (CS-108G, Cobe laboratories, Inc.) were used for all treatments. The duration of dialysis was 2–3 h. Each patient was dialyzed at the same blood flow rate (250 ml/min) and dialysate flow rate (500 ml/min) throughout the study. As machines without volumetric ultrafiltration monitoring (Cobe Century 2Rx) were used, ultrafiltration was minimized and calculated ultrafiltrate volume was replaced with saline during dialysis. Calcium-free dialysate (Green Cross Medical Corp.) contained sodium 135, potassium 2.5, chloride 108, magnesium 0.75, bicarbonate 30 mmol/l. The pH of the dialysate was 7.8. Plasma concentrations of total calcium, inorganic phosphorus, urea nitrogen, creatinine and ionized calcium were measured immediately before dialysis, at 1 h, and after dialysis. Hypocalcemic symptoms and signs were monitored continuously in all patients.

To calculate the actual clearance of dialyzer membrane, blood samples for urea nitrogen, total calcium, ionized calcium and inorganic phosphorus were taken from the arterial and venous lines of the dialyzer at 1 h of hemodialysis. The urea nitrogen clearance was 151 ± 32 ml/min; total calcium, 77 ± 31 ml/min; ionized calcium, 82 ± 28 ml/min; and phosphorus 101 ± 12 ml/min at blood flow of 250 ml/min. Volume of distribution for urea was assumed to be 60% of body weight in male and 50% in female. Statistical significance was determined by the paired t test. The correlation coefficients were determined by linear regression analysis. A p value less than 0.05 was considered significant.

Results

The clinical characteristics of the patients are shown in table 1. The peak calcium concentration was 3.28 ± 0.43 mmol/l; peak phosphorus, 1.65 ± 0.42 mmol/l; peak urea nitrogen, 16.8 ± 8.4 mmol/l; peak creatinine, 540 ± 274 μmol/l, total protein 72 ± 13 g/l; and serum albumin, 35 ± 3 g/l. The calcium concentration decreased to 2.92 ± 0.21 mmol/l with forced saline diuresis. The effect of saline diuresis with furosemide was limited, while the presence of severe renal failure prevents the administration of large volumes of intravenous fluids to hypercalcemic patients.

The systolic blood pressure was 145 ± 22 mm Hg and the diastolic pressure 88 ± 9 mm Hg before dialysis. The systolic pressure decreased to 118 ± 26 mm Hg and the diastolic pressure decreased to 76 ± 17 mm Hg at the end of dialysis. The systolic blood pressure was significantly decreased at the end of dialysis as compared to predialysis ($p < 0.05$). However, the diastolic blood pressure at the end of dialysis was not statistically different from that before dialysis.

The results for 8 dialyses in 6 patients are shown in table 2. The plasma calcium concentration fell from an

Table 1. Clinical characteristics of patients

Patients	Age, years	Sex	Weight, kg	Diagnosis
1	64	F	60	lung cancer
2	65	F	50	multiple myeloma
3	58	M	58	multiple myeloma
4	55	M	66	lung cancer
5	42	M	70	renal cell carcinoma
6	60	M	60	multiple myeloma

Table 2. Effect of calcium-free hemodialysis on plasma calcium concentration

Patient	Plasma calcium, mmol/l			Time, min	Kt/V urea
	pre-HD	HD 1 h	post-HD		
1	3.25	2.75	2.53	120	0.80
2	2.93	2.45	1.63	180	1.09
3	2.55	2.3	1.73	180	0.88
4	3.08	2.6	2.2	180	0.68
5	2.83	2.75	2.45	120	0.55
	2.83	2.48	2.13	150	0.69
	3.05	2.73	2.13	180	0.82
6	2.88	2.63	2.45	170	0.47
Mean ±SD	2.92 ±0.80	2.58 ±0.16	2.16 ±0.33	160 ±27	0.75 ±0.20

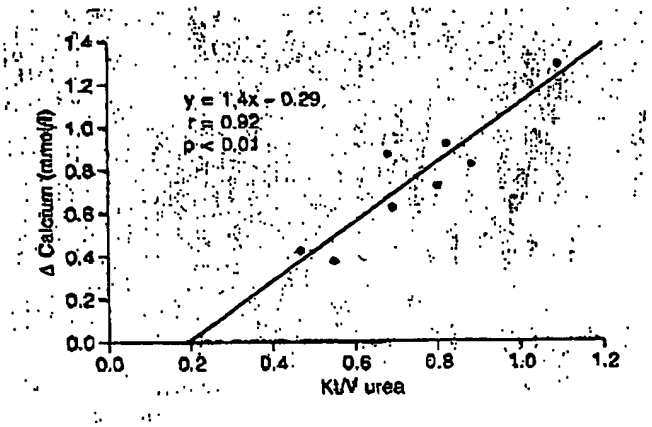

Fig. 1. Relationship between the changes in plasma calcium concentration and the Kt/V urea.

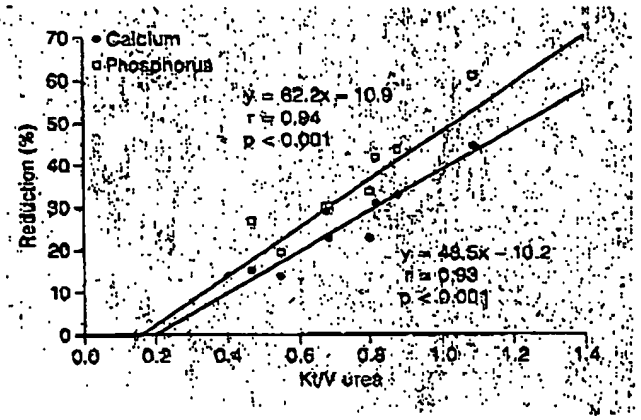

Fig. 2. Relationship between the percent reduction of plasma calcium and phosphorus and the Kt/V urea.

initial value of 2.92 ± 0.21 to 2.58 ± 0.16 mmol/l at 1 h of hemodialysis and to 2.16 ± 0.33 mmol/l following 2–3 h of hemodialysis. Mean hemodialysis time was 160 ± 27 min and mean Kt/V urea was 0.75 ± 0.2. The ionized calcium (n = 4) decreased from 1.44 ± 0.14 to 0.99 ± 0.2 mmol/l. Of the total plasma calcium, ionized calcium was 49.6 ± 4.4% before dialysis and 42.6 ± 9.9% after dialysis. No patient showed any hypocalcemic symptoms or signs during hemodialysis. There were no hypocalcemic signs even in the patient with postdialysis plasma calcium of 1.63 mmol/l. The ionized calcium concentration was not available in this patient after dialysis. The inorganic phosphorus concentration reduced from 1.56 ± 0.42 mmol/l before to 1.0 ± 0.36 mmol/l after dialysis. Clinical improvement, including improved mental status and decreased weakness, accompanied the decline in the plasma calcium during hemodialysis. Side effects included asymptomatic hypocalcemia and hypophosphatemia.

There was a significant positive correlation between the decrease in the plasma calcium concentration and the Kt/V urea ($y = 1.4x - 0.29$, $r = 0.92$, $p < 0.01$, fig. 1). A significant positive correlation between the percent reduction of total calcium and the Kt/V urea ($y = 48.5x - 10.2$, $r = 0.93$, $p < 0.001$, fig. 2) was also noted. The reduction rate of phosphorus was higher than that of plasma calcium ($y = 62.2x - 10.9$, $r = 0.94$, $p < 0.001$, fig. 2). Total calcium was decreased 26 ± 10% and the phosphorus was decreased 36 ± 13% with this amount of dialysis.

The survival of patients after treatment for hypercalcemia of malignancy was limited. Four of the patients died within 8 weeks after calcium-free dialysis. Although no statistical analyses of the response by different cancer types were performed due to the small sample size, the rates of decrease in calcium did not appear to be influenced by the type of cancer.

Discussion

The symptoms of hypercalcemia include generalized weakness, nausea, vomiting, polyuria, lethargy and stupor. Thus, early recognition and treatment of hypercalcemia are clinically important. The usual therapeutic measures in hypercalcemic crisis are based on an increase of renal calcium excretion (forced saline diuresis [6], glucocorticoids [7]) and on the reduction of calcium mobilization from bones (calcitonin [7], mithramycin [8], diphosphonates [9, 10]). Most therapies have been associated with limited efficacy and cumulative toxicity [11]. Furthermore, the combination of renal failure and hypercalcemia is a very difficult situation for the treatment. Treatment with intravenous saline results in a partial decrease in plasma calcium in most patients [2]. Part of the early reduction in plasma calcium is due to the dilutional effect of volume expansion, but salt and water loading leads to both an increase in the glomerular filtration rate and enhanced fractional excretion of calcium. However, forced saline diuresis may not be safe or effective, particularly in patients with advanced renal failure. Some patients in our study had been volume overloaded during saline diuresis with furosemide before calcium-free hemodialysis was started. Diphosphonates have been thought

of as the drugs of first choice for the management of malignancy-associated hypercalcemia [12]. However, caution should be used in patients with renal failure [13]. Furthermore, it may take 4–5 days to decrease plasma calcium to normal. Another therapeutic approach to hypercalcemia is the combination of calcitonin and glucocorticoids [7]. This combination is particularly effective in patients with myeloma and hypercalcemia. This combination is not uniformly effective in all kinds of hypercalcemia [18].

Patients with severe hypercalcemia, renal failure, cardiac failure, cardiac arrhythmia, and/or altered level of consciousness have a high morbidity and mortality. In such patients, consideration should be given to rapidly lowering the plasma calcium using calcium-free dialysis. The use of calcium-free dialysis combined with therapy for the underlying cause of hypercalcemia may improve morbidity and mortality of the patients. The maximum calcium elimination capacity of hemodialysis has been reported as 17-mmol calcium per hour, an 8-fold higher rate than forced saline diuresis and a 5-fold higher rate than the maximum of peritoneal dialysis [4].

In this study, plasma calcium concentrations fell from a mean value of 2.92 ± 0.21 mmol/l (range 2.55–3.25) to 2.16 ± 0.33 mmol/l (range 1.63–2.53) following 2–3 h of hemodialysis. As expected, plasma calcium concentration decreased significantly ($p < 0.001$). No patient showed any hypocalcemic signs during hemodialysis. Hypocalcemic signs were not evident even in a patient with post-dialysis calcium of 1.63 mmol/l. Mild hypocalcemia after dialysis was asymptomatic in all patients.

There was a significant positive correlation between the decrease in the plasma calcium concentration and the Kt/V urea. Decrease in plasma calcium concentration can be estimated as $y = 1.4$ Kt/V urea $- 0.29$. The rate of decrease in plasma calcium concentration in our study did not appear to produce adverse effects in any of the patients. There was also a significant positive correlation between the percent reduction of total calcium and Kt/V urea.

Adequate volume replacement during calcium-free dialysis is of importance, because systolic blood pressure falls significantly without net ultrafiltration in patients with hypercalcemia. In other reports, dopamine infusion has been required to maintain adequate systolic blood pressure [4]. Our patients did not show severe hypotension during calcium-free dialysis. Predialysis fluid overload in our patients may contribute to protective symptomatic hypotension during calcium-free hemodialysis.

Asymptomatic hypophosphatemia after dialysis was a problem to be solved during calcium-free dialysis. Only a small portion of the inorganic phosphate in the blood is bound to proteins. Although 85% is 'free', determination of the percent ultrafilterability of phosphate has consistently yielded as much as 95%, because plasma water and Donnan membrane effects reinforce each other [15]. The phosphorus clearance was higher than plasma calcium clearance in this study. Phosphate loss might be a major cause of the dialysis hypercalcemia in standard hemodialysis [16]. Since bone is the major body phosphate reservoir, it is postulated that as phosphate leaves the exchangeable bone pool due to a precipitous fall in the plasma phosphate concentration [17], concomitant calcium efflux from bone into the extracellular compartment can occur more rapidly in patients with hypercalcemia. Because phosphate therapy may benefit hypercalcemic patients with hypophosphatemia [11], addition of phosphate to the dialysate should be considered in patients prone to hypophosphatemia.

Monoclonal myeloma proteins have characteristic isoelectric points. Murray et al. [18] have reported a decrease in anion gap in patients with myeloma. This occurs because some myeloma proteins with a high isoelectric point will take up protons and become positively charged at normal serum pH. Therefore, chemical characteristics of myeloma protein can make a difference in the clearance of calcium or the ratio of ionized calcium during dialysis. No statistical analyses of the response by cancer type were performed due to the small number of patients. Further studies are required to determine whether the existence of myeloma protein or the extent of skeletal metastasis may influence the effects of calcium-free dialysis.

As expected, the effect of calcium-free hemodialysis was short-lived. Therapeutic measures to decrease osteoclastic bone resorption should be followed to maintain plasma calcium levels at normal. Calcium-free hemodialysis will be an option worth considering for the malignancy-associated hypercalcemic patients not responding to the hypocalcemic drugs. Calcium-free hemodialysis is also useful for complete avoidance of acetate in bicarbonate dialysis and for the use of citrate rather than heparin as an anticoagulant [19].

In summary, calcium-free hemodialysis would be an effective and safe therapeutic modality in patients with hypercalcemic crisis and advanced renal failure. Single 2- to 3-hour treatment with a calcium-free dialysate is safe, provided that predialysis plasma calcium is high. Calcium-free hemodialysis is indicated when the presence of

severe renal failure prevents the administration of large volumes of intravenous fluids to hypercalcemic patients. The amount of dialysis (Kt/V urea) can be used to predict the decrease in plasma calcium concentration during calcium-free hemodialysis.

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TI **Calcium-free hemodialysis** for the management of hypercalcemia
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DT Journal
LA English
TI **Calcium-free hemodialysis** for the management of hypercalcemia
AB The drug therapies for hypercalcemia of malignancy have been known to be assocd. with either limited efficacy or cumulative toxicity in patients with advanced renal failure. To establish the guidelines for the use of **dialysis** and to det. its optimal prescription for hypercalcemia, **calcium-free hemodialysis** was performed in 6 hypercalcemic patients with renal failure not responding enough to forced saline diuresis. **Calcium-free** dialyzate contained sodium 135, potassium 2.5, chloride 108, magnesium 0.75, **bicarbonate** 30 mmol/l. Mean **hemodialysis** time was 160 .+-. 27 min and mean Kt/V urea was 0.75 .+-. 0.2. Plasma calcium concns. fell from a mean value of 2.92 .+-. 0.21 mmol/l (range 2.55-3.25) to 2.58 .+-. 0.16 mmol/l at 1 h of **hemodialysis** and to 2.16 .+-. 0.33 mmol/l (range 1.63-2.53) following 2-3 h of **hemodialysis**. The ionized calcium (n = 4) decreased from 1.44 .+-. 0.14 mmol/l to 0.99 .+-. 0.2 mmol/l. No patient showed any hypocalcemic symptoms and signs during **hemodialysis**. The rate of decrease in plasma calcium did not appear to produce adverse effects in any of the patients. There was a significant pos. correlation between the decrease in plasma calcium concn. and the Kt/V urea ($y = 1.4x - 0.29$, $r = 0.92$, $p < 0.01$). We conclude that **calcium-free hemodialysis** is indicated when the presence of severe renal failure prevents the administration of large vols. of i.v. fluids to hypercalcemic patients. The amt. of **dialysis** (Kt/V urea) can be used to predict the decrease in plasma **calcium** concn. during **calcium-free hemodialysis**.

This is EXHIBIT E referred to in the
Declaration of Sheldon William Tobe, M.D.
sworn this 8th day of February, 2006

A Commissioner, Notary, etc.

NEIL HARVEY HUGHES, Notary Public, Province of Ontario,
limited to the attestation of instruments and the taking of
affidavits, for Ivor M. Hughes, Barrister and Solicitor,
Patent and Trademark Agents.
Expires March 30, 2007.